



IMPROVING MEDICINES FOR CHILDREN IN CANADA

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



Council of Canadian Academies
Conseil des académies canadiennes

Science Advice in the Public Interest

IMPROVING MEDICINES FOR CHILDREN IN CANADA

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

THE COUNCIL OF CANADIAN ACADEMIES

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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.

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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 "S 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.

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1

Introduction

- **Background and Purpose:
Children Are Different**
- **Charge to the Panel**
- **Panel's Approach and Methodology**
- **Organization of the Report**

1 Introduction

1.1 BACKGROUND AND PURPOSE: CHILDREN ARE DIFFERENT

Children have a right to health and well-being, and children who are ill need treatment that is appropriate for the age and stage of their developing bodies and minds. Medicines designed for adults may not be suitable for these needs. However, adult conditions are often prioritized over children’s therapies in discussions about the burden of disease; the feasibility of and expected benefit from research; and the marketability, development, and approval of medicines. As a result, children have historically been neglected in drug research and development and in Canadian regulations.

At one time, researchers included children in research only as a last resort. In recent years, this thinking has shifted. The current understanding is that including children in research is an important way of reducing inequities in health and improving the evidence base to inform medical practice. This perspective is in line with the *1989 United Nations Convention on the Rights of the Child*, to which Canada is a signatory. The Convention recognizes that children are entitled to special care, including health care, to “the highest attainable standard of health” (UN, 1989). This involves a balance between ensuring the availability of therapies for children that are known to be safe and effective and recognizing the challenges of conducting research in children.

Reflecting this paradigm shift, policy changes in the global medicines environment have raised the profile of and the expectations for research with pediatric populations (see Section 1.3.1). In the last decade, the World Health Organization (WHO) has sponsored an international initiative to “make medicines child size” (WHO, 2014b). Intended to stimulate awareness and information-sharing for the development and use of medicines for children, this campaign has paralleled reforms among Canada’s principal trading partner countries. As the international capacity for pediatric medicines research is strengthened, legislators have created laws that permit medicines regulators to make new and stronger standards in their policies. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have, over the last several years, both asserted the authority granted by the legislation to require studies with children and provided incentives for such research. There is evidence that these regulations and incentives have benefited children in these jurisdictions but not Canadian children.

Canada is in a position to align with changes to international regulation of pediatric drug development. In a study to investigate pharmaceutical drugs, the Senate of Canada (through the Standing Senate Committee on Social Affairs, Science and Technology) is pursuing the legislative aspects of improving access to medicines, and Health Canada, the regulatory authority, is actively responding to the findings of that ongoing investigation. To support increased research in Canada, Health Canada has recently created a public database of the clinical trials underway in Canada and has proposed a new orphan drug regulatory framework to guide the authorization and monitoring of drugs for rare diseases. At the time of the Panel's deliberations, new proposed amendments to the *Food and Drugs Act* were before the government, in Bill C-17. The proposed amendments would change the authority granted to Health Canada. For example, they would empower the regulator to recall drugs, require manufacturers to provide any information within their control to Health Canada, require changes to product labels, and impose enforcement for non-compliance (House of Commons, 2013). These efforts are not specific to drug treatments for children; however, they may be used to advance knowledge about and improve availability of drugs for children, as discussed later in this report. Furthermore, innovations in study methods are making it easier to generate new knowledge in ways that protect the interests of children of all ages. In this context, this assessment had the unique opportunity to examine comprehensively the current Canadian landscape, the state of knowledge of clinical pharmacology, and lessons learned from international experiences. The work of the Expert Panel fills a distinctive niche in the effort to advance pediatric medicines research in Canada.

1.2 CHARGE TO THE PANEL

Recognizing the importance of developing safe and effective medicines for children, the Minister of Health, on behalf of Health Canada (the Sponsor), asked the Council of Canadian Academies (the Council) 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. This assessment focuses on the ethical development of safe and effective therapeutic products — both pharmaceuticals and biologics, including vaccines (see Section 1.3.1) — for infants, children, and youth; examines gaps in the current state of knowledge; and identifies opportunities for strengthening knowledge of safe and effective pediatric medicines. 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. Panel members brought knowledge from the disciplines of pharmacology, epidemiology, public health, ethics, and pediatrics. 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.

Over 14 months, the Panel met in person five times to refine its assessment of the issue at hand. At the beginning of the assessment process, the Panel met with the Sponsor to acquire a full understanding of the charge and receive additional direction:

- Therapeutic products were to be interpreted to include human pharmaceuticals and biologics, including vaccines.
- The Panel's interpretation of pediatric populations was to encompass birth to 18 years of age, including pre-term newborns. Medicines that could be transmitted to infants and children through breastmilk were to be considered as part of the charge only when administered to the nursing mother as a route of delivery intended for the infant or toddler. The assessment was not to explore risks of unintentional transfer or maternal health more broadly.

- Best practices for ethically and scientifically sound drug studies was to include a range of alternatives to conventional clinical trials. Both established and emerging practices were to be considered. Although the charge suggests confirming safety and effectiveness, the Panel has interpreted this direction as the science for investigating or establishing safety and effectiveness.
- The assessment was to consider global efforts for all dimensions of pediatric clinical pharmacology, and not be limited to pharmacovigilance.

1.2.1 Scope

This report examines:

- evidence on safety, efficacy, and optimal forms and formulations of pediatric medicines;
- ethical issues related to involving infants, children, and youth in research;
- the full continuum of the drug approval lifecycle, including pre-market research, market approval, and post-market surveillance and monitoring;
- Canadian and international best practices in regulatory, monitoring, and surveillance systems;
- best practices in clinical trial and alternative study designs; and
- infrastructure that supports research, development, and surveillance specific to labelling of medicines for infants, children, and youth.

This report does not address:

- policies regarding drug plan coverage and provincial variation in costs or coverage of medicines;
- contributing factors and responses to drug shortages;
- the process for evaluating cost-effectiveness;
- a full range of known diseases or therapeutic products;
- drug discovery and commercialization;
- natural health products, such as vitamins and herbal remedies; or
- prescribing practices and decision-making related to therapeutic products by individual professionals, parents, and patients.

1.3 PANEL'S APPROACH AND METHODOLOGY

The Panel's assessment of the state of clinical pharmacology is based on various sources of evidence. Primary evidence-gathering activities included a review of:

- academic literature from peer-reviewed publications exploring human development, as well as research methodology and best practice for studies involving infants, children, and youth;

- publicly available government reports that describe regulatory context and specific policy initiatives;
- selected decision-making tools for pediatric clinical pharmacology; and
- other grey literature¹ relating to research involving infants, children, and youth.

In seeking the most relevant literature and emerging evidence, the Panel conducted keyword-based searches of published literature. The search strategies varied across different topics in the report, and evolved as the Panel assessed the availability of the most recent information. The Panel also sought information from leaders in industry and research practice. To do so, the Panel extended a targeted invitation to Canadian associations that represent diseases and conditions affecting children and to manufacturers engaged in the research and development of medicines for children. The objective of inviting such contributions was to ensure the Panel assessed any recent and emerging standards, especially on topics that appear less frequently in published literature, such as patient and family engagement in research and best practices in research. The response supplemented the literature search process, validating the findings and pointing to additional high-quality published evidence that was used in Panel deliberations. See Appendix for a list of organizations that responded to the Panel's invitation.

To further supplement the information obtained from the published literature and to enhance its contribution to the question, the Panel examined some original analyses of new evidence. The Panel commissioned an original analysis of prescription drug use claims in 2012 from private insurance plans, provided by IMS Health Canada Incorporated (IMS, 2013). In line with a similar method adopted in previous research (Abi Khaled *et al.*, 2003), the Panel examined this subset of prescription drug claims to characterize frequent medicine use in children in Canada.

This report is the result of the Panel's deliberations on the charge and the available evidence. The Panel's discussions generated original interpretations of and insight into the evidence. The report has undergone a formal peer review process to assure quality and objectivity; all comments from the reviewers were considered by the Panel, although not all comments resulted in revisions to the report.

1 *Grey literature* refers to various types of documents, produced by government, academics, industry, and other organizations, that are not controlled by commercial publishing (GreyNet, 2014).

1.3.1 Key Terms

The Panel has defined terms central to the charge, based on its interpretation of the Sponsor's interest. These definitions differ in some cases from traditional understandings of the concepts. The Panel's choices reflect a careful reading of the questions and, in some instances, a blend of definitions put forward in other sources.

Pediatric encompasses the stages of development, beginning with birth through infancy, childhood, and youth up to the age of 18 years. While other classifications are available to distinguish stages of development within this period (ACOG, 2013), the Panel adopted age ranges from internationally recognized standards (ICH, 2000a). The International Conference on Harmonisation (ICH) has established a range of categories that serve to mark the stages of human development: pre-term newborn (<37 weeks gestation); term newborn (0 to 27 days); infants and toddlers (28 days to 23 months); children (2 to 11 years); and adolescents (12 to 16 or 18 years, depending on region) (ICH, 2000a). While some concepts apply to subsets of the pediatric population, other issues concern the whole group. The terms *child* and *children* are used both for the whole pediatric population and, where specified, for the age group of 2 to 11 years.

Clinical pharmacology is the scientific study of all aspects of the relationship between humans and drugs to establish evidence to inform therapeutic use of drugs. Although clinical pharmacology is understood by some to be a unique medical subspecialty (Gray *et al.*, 2007), the broader science can engage a range of disciplines and professionals. Pediatric clinical pharmacology encompasses in-depth knowledge of human physiology and development associated with the absorption, distribution, metabolism, excretion, efficacy, and risks of drugs in children. Drug responses in real-world settings are part of what is studied in clinical pharmacology. This study involves various methods, including a range of clinical trial and alternative designs.

Therapies, in line with Health Canada's definition of drugs, include *biological products* (drugs derived from biotechnology or living sources) and vaccines, as well as *pharmaceuticals* (small-molecule drugs, mainly chemical compounds). Because similar issues arise in ensuring safety and efficacy of both prescription and non-prescription — or over-the-counter — medicines (e.g., HC, 2009a), both are included in the Panel's assessment. The Panel's assessment did not include medical devices, tissues and organs, or natural health products. The terms *drug*, *medicine*, and *medication* are used interchangeably to refer to therapies. In this assessment, the term *drugs* refers to medicines for therapeutic use and excludes discussion of recreational or performance-enhancing — and often illegal — use of pharmacologically active agents or substances.

Ethics is a broad discipline that explores and analyzes moral options in particular domains of enquiry. The focus of this assessment is on bioethics, the field of ethics concerned with the impact of advances in biomedicine on humanity and its environment. It is a constantly evolving multidisciplinary field of reflection and enquiry based on principles of justice, respect for persons, and concern for welfare. Research in pediatrics recognizes children's vulnerability and is premised on the belief that their best interests, dignity, and rights must be honoured and respected. Ethical issues in pediatric research are also critical because of past serious abuses of human rights in the name of research, sometimes involving children (Shuchman, 2013).

Drug studies include two types of investigation — *clinical trials* and *observational studies*. In a clinical trial, participants are assigned by the investigator to receive one or more health-related interventions according to a research plan or protocol in order to evaluate the effects of those interventions on health outcomes. Generally, in observational studies, investigators assess real-world drug use and health outcomes of patients receiving different interventions prescribed by a physician on an individual basis. Unlike clinical trials, participants in observational studies are not assigned to specific interventions by an investigator. Although the Panel's assessment focuses on drug investigations, clinical trials and observational studies can also examine procedures, devices, behavioural treatments, and other interventions (NIH, 2012a; WHO, 2013a).

Pharmacovigilance refers to the science and activities involved in detecting, assessing, understanding, and preventing drug-related problems including adverse events (WHO, 2002). The monitoring and ongoing analysis of benefits and harms in both pre- and post-market settings — before a drug is approved for sale and after it is available — are part of pharmacovigilance.

The charge from the Sponsor demands an exploration of safe and effective medicines. *Effective* medicines are those that produce a desired response in the real-world practice of medicine. In the context of drug research, the Panel has also considered the efficacy of medicines, which is the capacity to produce a desired effect, usually in controlled study situations (Artlett *et al.*, 2005). An effective medicine will produce that desired response while also satisfying standards for safety and quality. The Panel has focused on methods to ascertain efficacy (Chapter 5) and safety (Chapter 6), recognizing these as key components of effective medicines.

1.4 ORGANIZATION OF THE REPORT

The final report is an in-depth assessment of the state of knowledge regarding the relationships among clinical pharmacology, human development, and pediatric drug investigations. As such, it is intended as a tool for informing research programs and policy-making for government agencies and ministries as well as for interested researchers. This assessment may also be relevant to a variety of stakeholders concerned with science-based issues of significant public health importance and to individual health care providers in Canada. The Panel intends this assessment to inform the continuing dialogue about therapeutic products for children across Canada, internationally, and in many sectors.

Chapter 2 outlines how drugs are currently used in children and the current role of the regulator in guiding the development of medicines for children. This overview also identifies how legislation and regulation in the European Union and the United States have created different incentives for pediatric medicines research.

Chapter 3 introduces the best available knowledge about how human development affects the response to drugs.

Chapter 4 explores how that knowledge can be applied in drug development, with pediatric-specific forms and formulations.

Chapter 5 develops approaches for drug studies focused on efficacy, while Chapter 6 explores challenges and opportunities in drug studies focused on safety.

Chapter 7 synthesizes knowledge on the assessment sub-questions, highlighting Canadian strengths within each as applicable. The Panel's final reflections are also included.

2

Current Environment for Drug Development, Regulation, and Use

- **How Drugs Are Currently Used and Regulated for Children**
- **The Need for Research in Children**
- **Responding to the Need for Research**
- **Chapter Summary**

2 Current Environment for Drug Development, Regulation, and Use

Key Findings

- Infants, children, and youth in Canada benefit from medications for their health and well-being. Each year, about half are prescribed at least one medication. While most of these children take one or two medications per year, some children with serious health problems may take many drugs at the same time or may require drug therapy for long periods. They need access to drugs that are proven to be safe and effective for them.
- In Canada, few therapeutic products are approved for use in infants, children, or youth. As a result, off-label use of medicines — in the absence of appropriate dosing information, forms, and formulations — is common.
- Manufacturers are not required to generate or to provide data on drug safety and efficacy in children in Canada. Health Canada can request, but not compel, a manufacturer to submit results of studies with infants, children, and youth. When data are lacking, the label and prescribing information indicate insufficient evidence for use.
- There is no validated and comprehensive authority on which prescribers can base decisions about medicines for Canadian children. Prescribers make decisions about the use of drugs based on other evidence, including published studies, hospital-based handbooks and formularies, and their own experience. The scientific robustness of this information can be difficult to verify.
- In Canada, a regulatory incentive to manufacturers to submit data on pediatric use of drugs has had limited success. In the United States and the European Union, pediatric medicines research activity is encouraged, required, and monitored in ways that have improved the quality and quantity of research and of medicines for children. These legislative and regulatory measures offer lessons for Canada's lawmakers.

2.1 HOW DRUGS ARE CURRENTLY USED AND REGULATED FOR CHILDREN

In Canada, infants, children, and youth represent roughly seven million people and form approximately 20% of the population. According to the most recent Canadian census (in 2011), the majority are children (53%) and the smallest portion are infants and toddlers (11%), as shown in Table 2.1.

Table 2.1

The Population of Canadian Children

Age Group	Number of Children in Age Group	Proportion of Total Child Population (%)	Proportion of Total Canadian Population (%)
Infants and Toddlers (0–24 months)	756,311	11	2
Children (2–11 years)	3,694,842	53	11
Adolescents (12–17 years)	2,489,979	36	7

Data Source: Panel's calculation based on StatCan (2013a)

Newborns and infants and toddlers are shown as a single category in this table, as population counts are available by year only from the Canadian census. Note that age is recorded at last birthday in years.

Canada's overall health depends on the health of its children; every person's health in childhood plays a role in his or her well-being throughout life, and Canadian children of all ages benefit from drug therapies for improved health and well-being. Drugs play a role in treating common conditions that affect many children (Abi Khaled *et al.*, 2003; Zhang *et al.*, 2013). Each year, about half of children are prescribed at least one medication, according to recent estimates from British Columbia (Zhang *et al.*, 2013). Similar rates have been reported in Denmark and Italy (Thrane & Sorensen, 1999; Clavenna *et al.*, 2009). For children less than one year old, this rate was even higher, with 79% of children having received at least one prescription according to the British Columbia study (Zhang *et al.*, 2013). The rate in infants ranges from 60% to 92% in Italian, Danish, and Dutch children (Thrane & Sorensen, 1999; Schirm *et al.*, 2000; Clavenna *et al.*, 2009). Although in a given year, many children use one or two prescriptions, a small group of pediatric patients use more medicines to manage more complex health conditions (Abi Khaled *et al.*, 2003).

Some of these conditions affect children more than adults. Asthma, for example, is more prevalent in younger age groups than among older children and adolescents, and the prevalence declines in adulthood (Brownell *et al.*, 2012; StatCan, 2013b). Other illnesses, such as type 2 diabetes and rheumatoid arthritis, are more common among adults but still affect a significant percentage of children (StatCan, 2013c, 2013d). For those who live with a rare disease, defined by Health Canada as a condition affecting fewer than 1 person in 2,000 (e.g., cystic fibrosis), access to drugs that are safe and effective is no

less important (HC, 2012d). Although some illnesses may be remedied with a short course of drug therapy, other chronic conditions require longer-term or even lifelong treatment.

Although it is clear that Canadian children need and do take medicines to treat a range of conditions, the safety and efficacy of medicines for pediatric use is sometimes less certain. Children are not small adults, so small versions of adult medications will not suit. However, knowledge of how to optimize exposure and response to drugs for children with the right doses of medication is growing (see Chapters 3 and 4).

A study conducted a decade ago showed that more than 50% of Canadian children covered by private insurance plans received at least one prescription per year (Abi Khaled *et al.*, 2003). Among these, anti-infective agents, including antibiotics, were most common. In an effort to update this information, the Panel enlisted the help of IMS Health Canada Incorporated to review Canadian usage data from private pay-direct drug plans made in 2012 for children under the age of 13 years (IMS, 2013).² This reflects only outpatient claims made from January 1 to December 31, 2012, excluding the use of medicines in hospital settings and those paid by public medicare — including most vaccines — and reimbursement claims; they also exclude adolescents. For eligible insured children, a total of 5,682,997 claims were identified from 1,513,789 claimants; approximately 3.3 million Canadian children are eligible for drug claims in this sample. These data confirm that at a minimum, about half of children received at least one prescription drug within that year.

As little is known about the extent and type of pediatric drug use, this information offers new insight characterizing the current use of medicines by this group of Canadian children. Table 2.2 shows the top 40 drugs by share of claims; Figure 2.1 shows the drug classes that are most frequently used and the distribution of claimants and claims for each therapeutic area.

2 The Panel's assessment of available evidence indicated that use of medicines by adolescents may be more similar to use by adults; as such, the analysis focuses on younger age groups to offer new insight on use of medicines.

Table 2.2
Top Drugs by Share of Claims, 2012*

Drug	Share of Claims (%)
Amoxicillin	14.5
Methylphenidate HCl	7.4
Salbutamol	6.9
Fluticasone Propionate	5.8
Clarithromycin	4.0
Azithromycin	3.3
Cefprozil	2.5
Montelukast Sodium	2.4
Mometasone Furoate	2.3
Hydrocortisone Acetate	2.1
Lisdexamfetamine Dimesylate	1.8
Epinephrine	1.5
Amoxicillin–Clavulanic acid	1.5
Fusidic acid	1.4
Ciprofloxacin HCl–dexamethasone	1.4
Atomoxetine HCl	1.2
Cephalexin Monohydrate	1.2
Prednisolone Sodium Phosphate	1.1
Lansoprazole	1.1
Amphetamine Mixed Salts	1.0
Betamethasone Valerate	1.0
Risperidone	0.9
Sulfamethoxazole–Trimethoprim	0.8
Hydrocortisone	0.8
Ciclesonide	0.7
Ranitidine HCl	0.7
Erythromycin	0.6
Cefixime	0.5
Cholecalciferol	0.5
Mupirocin	0.5
Fusidic acid–Hydrocortisone Acetate	0.5

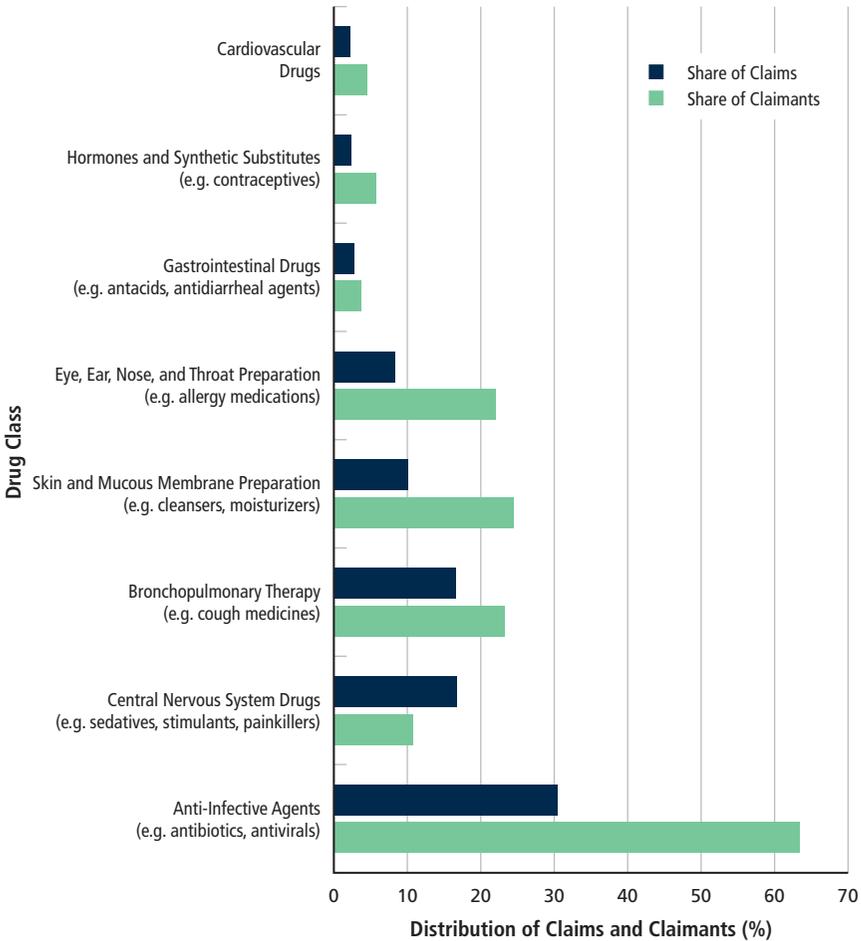
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Drug	Share of Claims (%)
Olopatadine HCl	0.5
Moxifloxacin HCl	0.5
Clonidine HCl	0.5
Beclomethasone Dipropionate	0.5
Vaccine—Hepatitis A and B	0.5
Nystatin	0.4
Gentamicin Sulfate	0.4
Hydrocortisone Valerate	0.4
Hydroxyzine HCl	0.4

Data Source: IMS Health Canada Incorporated Private Pay Direct Drug Plan database (2013)

* The Panel attempted to categorize the drugs by noting which have an approved pediatric indication. However, few are approved or not approved for all ages and stages of child development, so any consistent characterization of the label information is challenging and often not possible.

The analysis commissioned from IMS Health Canada Incorporated is similar to the results of the study by *Abi Khaled et al.* (2003) but not directly comparable because they use different age groups and drug classifications. However, when viewed together the reports suggest an increase in use of central nervous system drugs, which has also been observed in other studies (*Mayes et al.*, 2008; *Pringsheim et al.*, 2011b; *Sharma & Shaw*, 2012; *Zuvekas & Vitiello*, 2012). This category includes medicines prescribed for children to manage a range of conditions, including attention deficit hyperactivity disorder (*Purdue Pharma*, 2013; *Shier et al.*, 2013), pain (*CPhA*, 2013b), seizures (*CPhA*, 2013a), autism spectrum disorder (*Sharma & Shaw*, 2012), and schizophrenia (*Masi et al.*, 2006). Little is known about the effects — including harms — of long-term use of these drugs on development (*Meijer et al.*, 2009), including their impact on learning and cognition as well as metabolism and cardiovascular health (*APA*, 2013; *Ijff & Aldenkamp*, 2013). The potential for this research is elaborated in Chapters 5 and 6.



Data Source: IMS Health Canada Incorporated Private Pay Direct Drug Plan database (2013)

Figure 2.1

Types of Medicines Commonly Used by Children, 2012

This figure lists some of the types of medicines most commonly used by children under the age of 13 years. It indicates the classes of drugs that represent a majority of use in 2012. Some medicines are used by a large number of patients (e.g., anti-infective agents) while others are used by a smaller population of patients (e.g., central nervous system drugs). Share of claimants adds to more than 100% as claimants may have submitted for coverage of drugs from more than one category. Therapeutic classes are defined based on the pharmacologic-therapeutic classification of the American Hospital Formulary Service.

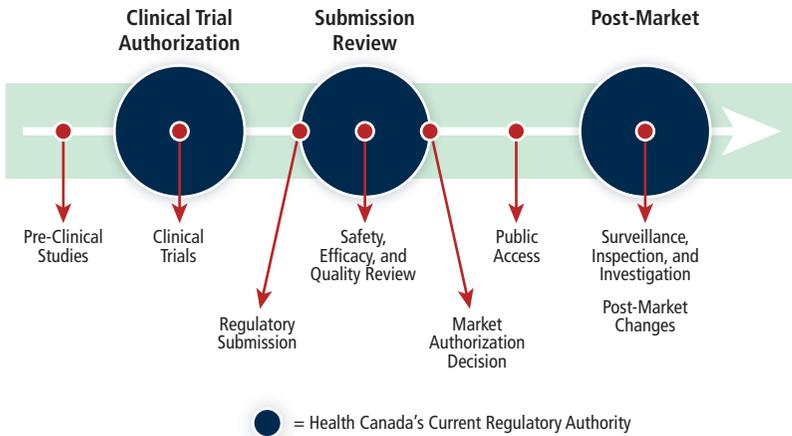
Despite the high utilization of drugs in children, many are not approved for such use by Health Canada and subsequently do not indicate in their associated consumer and prescribing information whether they can be safely and effectively administered to children. This situation of unauthorized drugs being commonly used in children often arises from the current regulatory framework for pediatric drug approval in Canada.

2.1.1 Regulatory Process for Medicines in Canada

To be authorized to sell a medicine in Canada, the manufacturer must provide the federal regulator, Health Canada, with evidence of the safety, efficacy, and manufacturing quality of the drug. Health Canada controls the market authorization of medicines in Canada through the provisions of the *Food and Drugs Act* and the *Food and Drug Regulations* (HC, 2006). To ensure that products meet the standards for safety and efficacy as specified in the legislation and regulations, Health Canada requires evidence from clinical studies on each proposed product. Standards for how research should be conducted are internationally recognized. The International Conference on Harmonisation (ICH), in which Canada plays a central role as an active observer, has developed a series of guidance documents. These specify guidelines that have been adopted by Health Canada and other regulatory authorities as requirements for human research on drugs.

Health Canada's authority is focused on several aspects of the research process. At each of these points, manufacturers must demonstrate to Health Canada that their products are safe, effective, and of appropriate quality. As shown in Figure 2.2 and described below, Health Canada's role is concentrated in:

- clinical trial authorization;
- submission review for market authorization; and
- post-marketing pharmacovigilance.



© All rights reserved. *Health Product Vigilance Framework*. Health Canada, 2012. Reproduced with permission from the Minister of Health, 2014 HC (2012g)

Figure 2.2

Health Canada's Current Health Product Review Process

New therapeutic products are evaluated by Health Canada before approval for sale and use in Canada. The diagram shows the stages in product review. Manufacturers conduct studies and submit data from trials of the drug at several stages: before testing in people (pre-clinical, generally from trials *in vitro* and in animals); testing for safety, efficacy, and quality in people (clinical trials); final data for authorization to market the drug (submission review); and follow-up studies after the drug is available for sale (post-marketing surveillance). This figure is not a complete statement of Health Canada's authorities. For example, the regulator has *de facto* influence over pre-clinical studies, is available to offer early scientific advice, and also inspects and investigates clinical trial sites and manufacturing sites to ensure that patients receive a consistently high-quality product. For more information, see Chapter 5 and Figure 5.1.

Health Canada has adopted guidelines that support the use of data from other jurisdictions in regulatory decisions (HC, 2003). These standards can reduce international duplication of effort and facilitate conclusions about safety and efficacy, but manufacturers decide whether to make a submission for authorization to sell a therapeutic product in Canada. While data may be submitted by manufacturers to Health Canada to support pediatric indications and labelling, the standards by which these are evaluated are not known and may differ from that of other regulators.

Under current legislation and regulations, a manufacturer is not required to provide data on drug safety and efficacy to support a label indication in children, even when it could be anticipated that the product is likely to be prescribed in children, regardless of whether the data were generated in Canada or abroad. Health Canada can request, but has no authority to compel, a manufacturer to apply for

a pediatric indication (HC, 2012f). If evidence on safety and efficacy for infants, children, and youth is not submitted, the label and prescribing information must indicate insufficient evidence for use in pediatric populations (Peterson *et al.*, 2011).

If the manufacturer does submit research data for approval of drug use in children, the manufacturer must include consideration of the variability introduced by human developmental processes and the associated needs for pediatric-specific medicines. Health Canada must rely upon evidence from clinical trials to satisfy this requirement (see Chapter 5 for more information about the regulatory requirements for trials). Clinical trials provide a standard of evidence that satisfies the need for data on safety and efficacy. As described in Box 2.1, the information from pediatric clinical trials can translate into clear guidance, both for the regulator and for practitioners, on how a drug can be used in treatment of children. However, drugs newly authorized in Canada infrequently include a pediatric indication, despite being prescribed for children and youth (Abi Khaled *et al.*, 2003).

Box 2.1

Pediatric Use of Fluticasone — Case Example

Fluticasone, among the most commonly prescribed drugs for Canadian children, is one of few with an evidence base available to the regulator, demonstrated safety and efficacy, and clear guidance to practitioners on appropriate use in pediatric populations.

Fluticasone is used to treat asthma and prevent inflammatory airway disease in adults, adolescents, and children. It consists of a corticosteroid that is inhaled to reduce and control inflammatory responses in the lungs. The medication is generally considered safe because of its low systemic bioavailability (i.e., the systemic concentration of the drug is minimal after topical inhalation). The drug is currently marketed under a range of brand names by both the innovator manufacturer and by generic companies, but is commonly known as Flovent[®] HFA (inhalation aerosol) and Flovent[®] Diskus[®] (inhalation powder).

Fluticasone was approved in 2004 by the U.S. FDA for use in adults and adolescents 12 years and older; the indication was extended to include children 4 to 11 years of age in 2006. In Canada, Flovent[®] Diskus[®] was approved in 1998 and Flovent[®] HFA in 2001. As of 2012, the Canadian product monograph notes that the drug is approved for use in children 4 years and older for Flovent[®] Diskus[®], and 12 months and older for Flovent[®] HFA (GSK, 2013).

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Fluticasone was approved for adults and adolescents based on three randomized controlled trials (RCTs) involving 980 patients. The studies found the drug to be effective compared to a placebo, and one of the studies also found the drug reduced the dose needed for patients taking prednisone — an oral corticosteroid used to treat inflammatory diseases (Noonan *et al.*, 1995). The indication was extended to children 4 to 11 years of age based on efficacy demonstrated in an additional RCT of 241 patients from these age groups and additional studies confirming low systemic bioavailability (CDER, 1997; GSK, 2010). Studies in children report evidence of efficacy in controlling asthma symptoms, but there is mixed evidence on the negative effects related to use of inhaled corticosteroids, including delayed growth and diminished cortisol concentrations (Turktas *et al.*, 2001; Allen, 2002; Carlsen *et al.*, 2005; Ducharme *et al.*, 2009; GSK, 2010).

The FDA has reported that, between 2004 and 2010, there were 23.1 million Flovent® HFA prescriptions dispensed for 6.4 million unique patients, of which 40% were 16 years and younger (CDER, 2010). The Panel's analysis of data indicates that fluticasone was the fourth most commonly prescribed drug for children in private direct-pay plans in Canada in 2012 (Table 2.2), representing almost 6% of claims.

2.1.2 What Is Off-Label Use?

Drug approval is specific to the dosing, route of administration, package labelling, formulation, method of manufacture, and indicated conditions for a product.³ Off-label is shorthand for a use that differs from that approved by Health Canada and can refer to any departure from that authorization.⁴ For example, a product might be prescribed for a different condition than indicated or used for a patient of a different age (Kimland & Odland, 2012). Table 2.3 outlines some off-label practices and examples of each.

³ Together, all of the written material that accompanies, supplements, or explains the product is called the *label*. However, *label* is often used to mean the final approved regulatory information, especially the indication. The packaging and *product monograph* providing prescriber and consumer information often fail to specify directions for children, or state that safety and effectiveness have not been established in children. This signifies that Health Canada was not given data on safety and efficacy for pediatric use, whether these data exist or not. As a consequence, a prescriber or parent reading product packaging or monographs will find relatively few that indicate whether a medication can safely be given to a child and in what dosage.

⁴ Distinct from off-label use is the prescribing of unlicensed products, those without any approval from the regulator. Unlicensed products are rarely available in Canada, as they cannot be sold. As in the case of off-label products, the lack of approval for an unlicensed product might be the result of a manufacturer not applying for approval in Canada and does not necessarily reflect an absolute lack of evidence on the safety and efficacy of pediatric use of a drug.

Table 2.3

Off-Label Practices

Off-Label Practice	Intervention	Authorized Use (On-Label)	Off-Label Use
Using a medication for a different age than approved.	Mometasone by inhalation — a preventive agent used alone or in combination.	Ages 12 years and over for the management of asthma.	Children under 12 years.
Using a medication for a different condition than approved.	Diane®-35 — contains cyproterone and ethinyl estradiol, which regulate hormones that affect skin.	Short-term treatment of acne in young girls.	Contraception.
Using a medication in a different form than approved.	Lopinavir/ritonavir for treatment of HIV-1 infection.	Film-coated tablets in varying strengths for treatment of HIV/AIDS.	Tablets crushed and mixed with food to improve palatability.
Using a medication through a different route of administration than approved.	Epinephrine to relax breathing in case of allergic reactions and anaphylaxis.	Intravenous injection.	Inhalation of mist formed from the liquid using a nebulizer.
Using a medication in the absence of pediatric information.	Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine.	Management of depression in adults.	Children under 18 years.
Using a medication even though contraindicated for children.	Celecoxib, a nonsteroidal anti-inflammatory drug.	Short-term management of acute pain in adults, including rheumatoid arthritis.	Juvenile idiopathic arthritis.

Data Source: Abi Khaled *et al.* (2003); Zhang and Sanguebsche (2005); Best *et al.* (2011); Vlahovic-Palcevski and Mentzer (2011); Kimland and Odland (2012); AbbVie (2013); CPhA (2013c); EMA (2013a); HC (2013a); Lilly (2013b); Pfizer (2013); Sellers (2013)

2.1.3 How Common Is Off-Label Use Among Pediatric Populations?

Estimates of the prevalence of off-label use vary. In a recent review of hospital and primary health care in European countries, Kimland and Odland (2012) found the majority of children had received at least one drug outside of authorized use. For inpatient care, the prevalence of off-label use was estimated to be between 10% and 65%, while Shah *et al.* (2007) found 78% of patients in 38 pediatric hospitals in the United States received at least one drug off-label. For outpatient care, between 11% and 31% of prescriptions were found to be off-label (Kimland & Odland, 2012). A recent study of visits to physicians by children and adolescents for antidepressants in the United States found

that fewer than 1 in 10 (9.2%) resulted in a prescription that met the age and indication of the regulator's approval (Lee *et al.*, 2012); in other words, 90% of appointments involved off-label prescribing of antidepressants. From international contexts, off-label prescribing is understood to be more common among younger age groups (Chalumeau *et al.*, 2000; Vlahovic-Palcevski & Mentzer, 2011; Kimland & Odland, 2012) and in intensive care settings compared with general practice (Chalumeau *et al.*, 2000; O'Donnell *et al.*, 2002).

A Canadian study of adult medicine use indicated that as much as 11% of all medicine prescribing is for off-label uses and 79% of off-label use is not supported with strong evidence (Egualo *et al.*, 2012). No known studies explore how off-label prescribing for children in Canada differs by condition or drug class. In fact, the extent of off-label use among the Canadian pediatric population is unknown, although common speculation is that as many as 75% of all prescriptions may fall outside regulatory approval (Senate, 2012). Box 2.2 provides a Canadian example of evidence that suggests a drug being prescribed off-label for use in children. Specific numbers are difficult to estimate because the information on prescriptions dispensed to children is spread across several different sources as hospitals, retail pharmacies, and public and private drug plans maintain independent records. Furthermore, outside of hospitals, data on prescriptions are rarely connected to a diagnosis. A patient record in a doctor's office will state what condition or symptom is being treated and document patient age and weight, but the pharmacy record will indicate only which drug was dispensed. From the prescription record alone, it is difficult to evaluate whether a drug was provided for an approved use (Abi Khaled *et al.*, 2003).

In a recent study of use of medicines for children at a Canadian hospital, Doherty *et al.* (2010) examined whether prescribing was within the specifications of the approval documented in the product monograph. By examining hospital charts, which contain more information about the diagnosis than a prescription record, the authors were able to investigate whether the intended purpose aligned with the authorized use. They found that almost 60% of prescribing was off-label. However, recognizing that many practitioners turn to other information for children's medicines, the investigators also used a pediatric prescribing reference — the SickKids *Drug Handbook and Formulary* (see below) — as an alternative standard for evaluating the use of medicines. When prescribing, as recorded in the hospital charts, was compared with the recommendations in the SickKids reference, less than 10% of prescribing was outside the guidelines (Doherty *et al.*, 2010).

Box 2.2

Pediatric Use of Olanzapine — Case Example

Olanzapine was first approved for use in the United States and Canada in 1996. It is used in adults for the treatment of schizophrenia, related psychotic disorders, and bipolar disorder. Olanzapine selectively dampens the effects of certain neurotransmitters (e.g., dopamine, serotonin) to control psychosis. However, its precise mechanism of action is unknown. It is sometimes referred to as an atypical antipsychotic drug because it is believed to have fewer of the extrapyramidal side-effects that cause impairment or involuntary initiation of movement associated with older antipsychotic medications. Olanzapine is currently marketed under a range of brand names both by the original manufacturer and by generic companies.

Olanzapine was approved by the U.S. FDA for use in adolescents ages 13 and older in 2009, principally based on two RCTs — one involving adolescents aged 13 to 17 with schizophrenia, and another involving adolescents aged 13 to 17 with bipolar disorder (CDER, 2009a). Due to safety concerns and a disparity in efficacy outcomes between two principal study sites, the FDA also required the manufacturer to complete additional studies before approving the drug for use in adolescents (CDER, 2009b). However, in Canada, olanzapine is not indicated for patients less than 18 years of age, and the related Canadian product monograph carries a warning that efficacy and safety have not been established for this population, stating greater frequency of adverse events in adolescents as a primary concern (Lilly, 2013a). Data on use of olanzapine by adolescents with schizophrenia and bipolar disorder were submitted to the European Medicines Agency (EMA) in 2008, but the drug was not granted approval. The label information for products marketed in the European Union was updated with safety information from those pediatric studies (EMA, 2013d).

Despite the fact that neither the United States nor Canada has approved olanzapine for use in children under 13 years of age, researchers reported a ten-fold increase in the number of newer antipsychotics (including olanzapine) used in children under 14 years old in British Columbia between 1997 to 2007 (Therapeutics Initiative, 2009). It is believed that prescribing in this age range is not only for the treatment of schizophrenia, related psychotic disorders, or bipolar disorder, but also for behavioural disorders, an indication that is also off-label (Therapeutics Initiative, 2009). The prescribing of this drug to children points to a misalignment between prescription information and the prescribing habits of physicians treating children, and represents an example of common off-label practices.

The *Drug Handbook and Formulary* is a reference prepared by the Drug and Therapeutics Committee of the Hospital for Sick Children (SickKids) in Toronto and widely known as the SickKids *Drug Handbook and Formulary*. Its policies and recommendations are developed and approved by the multidisciplinary committee as rational drug therapy. The formulary⁵ is self-supporting with proceeds of sales outside the hospital. This reference provides information for hospital practitioners about recommended use of medicines in pediatric populations. The record for each drug is authored by pharmacists with the hospital drug information service, based on published research, but also drawing on in-house expertise. The recommendations are evidence-based, reflecting up-to-date knowledge about pharmacokinetic and pharmacodynamic implications. The handbook is published annually and updated as the available evidence changes (E. Lau, personal communication, 2014). This is one example of a hospital-specific drug handbook and formulary.

Prescribers look to a range of resources to inform prescribing. These resources include the product monograph, many of which are compiled in the *Compendium of Pharmaceuticals and Specialties* (the CPS), published by the Canadian Pharmacists Association in printed format (updated annually) and online (updated continuously). Manufacturers are invited, but not required, to submit approved monographs for inclusion in the CPS. Alongside the monographs provided by manufacturers, the CPS includes any Health Canada advisories that concern the product and also publishes monographs authored by the editorial staff, based on independent literature sources. Among these sources are clinical practice guidelines, primary literature, and manufacturers' product monographs.

The CPS illustrates some of the challenges in synthesizing knowledge about medicines for developing children. In product monographs, the indications section may not state whether the drug is approved for use in children; the warnings and precautions sections specify any known safety information or lack of clear safety information for children (whether the indication includes children or not); and the dosage guidelines may or may not further reveal whether there are options for prescribing in pediatrics. Some drugs that are approved for use in children may not list pediatric uses among the indications, but a dose for an approved pediatric indication could appear in the dosage section without being included in the indications section. Among the drugs that are authorized for use in children, most product monographs name conditions or other medicines that are ill-advised in combination with

5 A *formulary* is a list of drugs, often specifically recommended for use or covered under a particular health insurance plan.

the product. Many monographs describe how the use of a product may change across developmental stages. Medicines are, in several cases, recommended for some age groups and not others. Although some products are authorized for use in children and others are contraindicated for some portion of the pediatric population, the majority are stated as having unknown safety and efficacy among children (Uppal *et al.*, 2008; Doherty *et al.*, 2010).

Reviews from the United States (Field *et al.*, 2013) and Australia (Tan *et al.*, 2003) have found several limitations of product labels as used in those jurisdictions — including inadequate and inconsistent pediatric dosing information. The Panel’s analysis of the CPS supports similar observations in Canada. Product monographs are not structured in a way that clearly communicates the relevant information for treating children, and the language is often inconclusive. Given these challenges with product labels, many clinicians look to the published literature (Gaifulina, 2011; Field *et al.*, 2013) and to clinical practice guidelines within their specialties; however, these resources will not necessarily provide the same information on benefits and harms.

Clinicians may turn to one of many hospital-based pediatric references and formularies (Dayneka, 2003). This type of pediatric-specific resource may be a source of credible information on prescribing for infants, children, and youth, when it is based on peer-reviewed evidence. However, the Panel noted that the compilation of published evidence is susceptible to publication bias, as research finding safety issues and lack of efficacy is more likely to remain unpublished (Dwan *et al.*, 2008). In addition to using peer-reviewed evidence, hospital formularies sometimes recommend dosing guided by expert opinion, which is commonly understood to be a lower standard of evidence. Formularies developed by hospitals represent drugs available for use at a single institution and are not endorsed nationally or by subspecialty physician organizations. Furthermore, prescribing practices may or may not align with the official prescribing information as stated in the product monograph. Although they are based on the recommended usage for practitioners within a specific hospital, some formularies are being used beyond the hospital for which they are official policy. There are no known evaluations of how such references contribute to better practice or improved outcomes.

Clinicians may also turn to drug-information resources such as Lexicomp[®], an online source of clinical content available for practitioners through Wolters Kluwer Health Clinical Solutions. While there are data about the adoption of Lexicomp[®], there are no known evaluations of how such references contribute to better practice or improved outcomes.

In other countries, nationally sponsored reference documents have focused on pediatric prescribing. The *British National Formulary for Children* was developed from multiple sources, including the material submitted to the regulator for authorization of the drug. However, the formulary “also includes a great deal of advice that goes beyond marketing authorizations (product licences). This is necessary because licensed indications frequently do not cover the clinical needs of children” (BNF, 2013). The formulary also integrates the contributions of expert advisors as well as primary literature and other reference sources (Elias-Jones & Rylance, 2005; BNF, 2013). The Netherlands has also invested in creating a national formulary (Ceelie *et al.*, 2011) as part of the national medicines policy. The *Australian Medicines Handbook* now offers a *Children’s Dosing Companion* as a supplement (AMH, 2013a, 2014). The content, which is evidence-based and peer-reviewed, includes dosing information arranged by indications and by age group. Each monograph also specifies any uses that are off-label and if there are other preferred treatments for any indications (AMH, 2013b). These resources, which are based on a range of information beyond the data submitted for regulatory approval, are consistently available in multiple formats and updated regularly.

The resources available to Canadian prescribers are, in many cases, ambivalent about the appropriateness of drugs for all ages and stages of child development. Although there are several sources of information, there is no validated and comprehensive authority on which prescribers can base decisions about medicines for children. In order to meet children’s need for medicines, practitioners must look beyond the product monograph to pediatric-specific references that consolidate reliable evidence. International examples, in contrast, suggest there may be a way to combine the approved information with evidence from other sources. Section 2.3 introduces some of the options for improving the available information base for decisions about medicines, including the regulator requiring complete submissions of all information about the drug in question.

2.1.4 Is Off-Label Use Inappropriate?

Off-label use is not illegal in Canada, although it carries some risks.⁶ The potential harm to the patient is exposure to an ineffective product or dosage as well as unknown or unintended side-effects. When a drug is approved, the benefits are judged to outweigh any known harms associated with use,

6 Health Canada does not regulate off-label use; however, the *Food and Drug Regulations* prohibit manufacturers from promoting off-label uses of drugs (GoC, 2013). Similarly, the federal regulator in the United States does not regulate individual prescribing practices. The American Academy of Pediatrics has recently provided a policy statement clarifying that off-label use is not improper or illegal and is often required to give the most appropriate treatment of pediatric patients (AAP, 2014).

based on use in a particular way and for specified purposes. Any deviation from the therapeutic approach recommended may change the benefit–harm profile for a drug. Off-label use is associated with a greater risk of adverse events and more serious side-effects than approved use (Vlahovic-Palcevski & Mentzer, 2011; Kimland & Odland, 2012; Bellis *et al.*, 2013). Altering the recommended use — such as changing the form of the medicine (e.g., by crushing tablets and mixing with food) — may also reduce the medicine’s benefit to the patient (Best *et al.*, 2011) (see Chapter 4 for further explanation of this idea).

The consequences of off-label use may have both professional liability and moral implications for the prescriber. Practitioners have an ethical obligation to provide information about a treatment they are prescribing and are required to communicate the benefits and harms of any prescription to the patient or, in the case of minors, to the parent/guardian. Off-label prescribing may involve, by nature, less certainty about that evidence. If a drug is known to have an unfavourable harm–benefit profile in adults, clinicians may be unable to confidently prescribe it to children in an off-label context. Furthermore, the harm–benefit profile may be different in children and adults (Ungar, 2012). Despite these ethical implications, most practitioners prefer to treat with off-label therapies rather than to leave a patient without any treatment (Bright, 2006).

Off-label prescribing is sometimes supported by other evidence; that is, Health Canada may not have authorized a particular use, but safety and efficacy information is sometimes available from sources other than the Canadian drug label (described earlier), especially once a drug is on the market. Hence, some researchers distinguish between *well-founded* off-label prescribing based on evidence, such as that published in peer-reviewed research, practice guidelines or handbooks, and *ill-founded* (disputable) prescribing (Gazarian *et al.*, 2006; Gijzen *et al.*, 2009). Box 2.3 describes a case in which information readily available from other jurisdictions could form the basis for well-founded off-label use in Canada.

Box 2.3

Pediatric Use of Celecoxib — Case Example

Celecoxib was first approved in the United States in 1998 for use as an anti-inflammatory. This particular medicine offered an improvement on similar products with a reduced potential for serious gastrointestinal events (CPhA, 2013b).

continued on next page

Celecoxib is marketed under the brand name Celebrex[®]. In 2002, the manufacturer initiated an RCT in patients with juvenile idiopathic arthritis (Pfizer, 2008). Based on the results of this study, an FDA Advisory Committee voted 15 to 1 in favour of a label extension. In December 2006, the U.S. FDA approved extending the Celebrex[®] label to include treatment of juvenile idiopathic arthritis in populations aged 2 years and older, stating “[w]hile there are other medicines approved for the treatment of this disorder, for some children they may have limited effectiveness or cause intolerable side-effects. Celebrex[®] will be a needed additional treatment option for children” (FDA, 2006).

In Canada, Celebrex[®] was approved for market in 1999. Despite changes to the labelling of the drug in the United States, the Canadian product monograph for Celebrex[®] still carries a contraindication for its use in patients under the age of 18 years (Pfizer, 2013). In addition, under its indicated uses, the product monograph states that Celebrex[®] does not have safety and efficacy established in the pediatric population. As a consequence, use of Celebrex[®] in pediatric patients in Canada is off-label, whereas in the United States it is an approved use.

This is one example of a misalignment between prescription information available to physicians treating children in different jurisdictions that could be used for labelling in Canada, and thus represents a missed opportunity for care.

2.1.5 Improving Product Knowledge by Monitoring Off-Label Use

Surveillance and analysis of off-label use would be one way to develop a better understanding of the safety and efficacy of medicines. Observing off-label use provides information on populations that might not have been included in clinical trials for ethical and practical reasons. As a consequence, there are often little or no data on how those groups are likely to respond to a drug. Children are often among the groups excluded from pre-market research. Even when pediatric studies to determine safety and efficacy have been conducted, they may not have examined impacts among subgroups of the pediatric population, such as those with additional conditions (co-morbidities) or receiving other prescriptions. Closely monitoring the real-world use of products among these diverse populations is a potentially rich source of data about safety and efficacy. However, there are additional challenges in collecting and using the information about real-world use. The current Canadian system involves limited and informal channels for safety reporting (described in detail in Chapter 6). As a result, the poor quality of information currently generated from off-label use means that little or no knowledge about product safety and efficacy is systematically gained in a timely manner from that experience.

Later chapters will explore what methods of study, including those that go beyond conventional clinical trials, might present more flexible and helpful evidence about medicines for Canadian children.

2.1.6 Political and Social Factors Influencing Drug Use in Children

Many factors — such as geography, cost, and personal preferences — can influence which drugs are made available and actually used by a patient. These factors operate at the levels of the provincial health care system, the health care provider, and the patient and their family. This report focuses on the available science that informs the regulator’s decisions, but these other factors become dominant once the product is approved for sale.

Unlike other forms of health care, access to medications is not guaranteed by the *Canada Health Act*. Evaluations of relative benefits and harms are outside Health Canada’s mandate. After approval by Health Canada, access to prescription medicines is mainly governed by provincially administered public drug plans, by private sector drug plans, and through self-payment. Currently, the inclusion of children in provincial drug benefit schemes varies widely across Canada (Ungar & Witkos, 2005). Private health insurance plans, such as those provided as an employment benefit, continue to be the main source of coverage for medications for many Canadian children (CIHI, 2013).

Public and private drug plans determine which drugs will be covered. Plan members are sometimes required to share the cost of the medication through some form of co-payment or deductible. For medicines that are not approved on drug plan formularies, the full cost of the medication is an out-of-pocket expense for the family or caregiver.

In Canada, recommendations on which drugs to include in provincial drug formularies for all provinces except Quebec are prepared by the Canadian Drug Expert Committee (CDEC) appointed by the Common Drug Review (CDR) program of the Canadian Agency for Drugs and Technologies in Health (CADTH) (CADTH, 2013). Although independent of Health Canada’s assessment, CDEC uses similar information to Health Canada in its evaluation process, such as clinical drug safety and efficacy data provided by the manufacturer. In addition, the CDR also considers evidence of cost-effectiveness submitted by the manufacturer. In developing its report, the CDEC reviews additional research, input from patient groups, and the cost and therapeutic benefit of the product relative to existing therapies. That report, with its recommendations, is then considered by the CDR-participating drug plans in making their formulary decisions. The outcome of the CDR is often narrowing the product label,

by suggesting formulary coverage of a drug for a subset of the population or for a more limited indication. Data are often not reported at a level of detail to allow for objective interpretation of benefit and harm for different subgroups.

These recommendations, therefore, inform drug plan listings. While provincial drug plans may consider the CDEC's recommendations, they are not obligated to follow them. Some provincial drug plans perform their own review of the evidence before deciding whether to include a drug in the provincial formulary. The CDR reviews are one input to this process, alongside the priorities and resources of each plan. Disparity in the uptake of recommendations, and in the timing of such uptake, can create variation among provinces in regard to which medicines are covered under publicly financed plans. This is intensified by differences between public and private coverage, both in terms of who has coverage and what is covered (Ungar & Witkos, 2005). The ultimate consequence is disparity in access to medicines. Often a public or private plan will not provide coverage for a patient from an age group outside the approved indication. Hence, off-label use in pediatrics may often not be covered.

At the health care provider level, prescribing practitioners decide which treatment is best for each patient. As described earlier in this chapter, they may rely on evidence from the product monograph but also from other sources, especially in off-label prescribing. They may also be influenced by personal clinical experience with the potential benefits and harms of different products. At the patient level, an individual patient's needs and preferences ultimately influence how closely prescribed drug regimens are followed, within the options provided. Especially in the case of dependent children, treatment often involves a broader circle beyond the individual. Family and caregivers influence, or in some cases make, decisions about treatment options. Those decisions, in turn, impact the lives of individuals surrounding the patient (Ungar & Gerber, 2010).

Thus, after Health Canada has accepted the safety and efficacy of a drug, the decisions by provincial and private drug plan managers, prescribers, patients, and their caregivers influence whether and how a drug is ultimately used. Determinants include how the drug compares to other treatments, patient-relevant outcomes, cost, longer-term impacts on non-health outcomes, and personal preferences.

2.2 THE NEED FOR RESEARCH IN CHILDREN

The remedy for the lack of approval of pediatric indications and subsequent off-label use is to carry out research in children so that safe and effective drugs are approved for use. As well as informing drug therapy for pediatric populations, clinical research can provide additional benefits such as early

access to experimental treatments (Yusuf & Cairns, 2012). Many clinical trials involve Canadian children, although the subsequent benefit to Canada's children is not entirely clear, as described later in this chapter. Health Canada has recently provided public access to a database of information on trials that it has reviewed (HC, 2013b). However, the database includes limited details about each investigation, such as the protocol number and title, drug name, medical condition, and study population. Health Canada has also declared their pursuit of mandatory disclosure of trial information through an existing registry. Although public access and trial registration are not exclusive to pediatric trials, these changes may provide particular benefit to research with children.

Open access to data from trials conducted with children can encourage more sharing of research methods and results with other researchers and with the public (HC, 2012c, 2012e). WHO operates a searchable platform of clinical trials with data on clinical trials gathered from 12 registries around the globe (WHO, 2013a). In 2010, the Maternal Infant Child and Youth Research Network (MICYRN) published an analysis of the pediatric clinical trials in the WHO platform (Junker, 2010).

The Panel has considered data from the MICYRN analysis in its assessment of the extent of pediatric research in Canada. An update to the 2010 analysis was conducted using a similar methodology, based on a search of the WHO platform, and was presented to the Panel by Dr. Anne Junker, the Scientific Director of MICYRN. The findings of that research show that many clinical trials do include Canadian children notwithstanding the challenges in pediatric medicines research. At the time of the Panel's analysis (April, 2013), the WHO platform included information on 9,059 clinical trial sites actively recruiting participants up to 18 years of age. At that time, the United States was hosting the largest number of trial sites including pediatric participants — approximately 43% — while Canada hosted 8% (data not shown).

To provide a single portal for detailed information about individual investigations, the WHO platform draws information from various registries and also gives a snapshot of clinical trial activity overall. Although the Auditor General of Canada recently made recommendations to Health Canada concerning improving transparency of all ongoing trial activity (OAG, 2011), no such registry currently exists in Canada. Investigators may voluntarily register their research with platforms operated by the United States (www.clinicaltrials.gov) and Health Canada encourages but does not require them to do so. In fact, Health Canada currently has no formal requirement for public disclosure — for example, in an existing registry — regarding either protocols of trials underway in Canada, or trial results once completed, except for those trials funded by the Canadian Institutes of Health Research (CIHR).

There is broader interest in more complete disclosure of research activity. The AllTrials initiative is a recent collaboration of journals as well as academic and research institutes encouraging all trials to be registered and all results be reported (AllTrials, 2014). Public funders and publishers of research require public registration of trials they support,⁷ yet private manufacturers make their own decisions about publishing results. A trial registry would provide a more complete and accurate picture of the benefit and potential harm of products; it might capture patients who were dropped from the study and those for whom no results are indicated in the data submitted for approval. Furthermore, a registry would include failed trials (negative results) and results for drugs that were never submitted for approval or were denied approval to sell in Canada. The WHO platform and the Health Canada database can each contribute to improved transparency around clinical trial research. A repository for trial results, for example, one that would enable meta-analysis, is an altogether different structure. The Panel is not aware of any such resource available on trials conducted in Canada.

Infrastructure that enables knowledge sharing can address some of the challenges in conducting clinical research. Clinical trials are known to be costly and complex, especially for pediatric medicines (Matsui *et al.*, 2003; Rieder, 2003; Li *et al.*, 2007; Vanchieri *et al.*, 2008). The Panel was informed of several initiatives to improve Canada's appeal as a location for pediatric clinical trials. MICYRN links 19 health research organizations based at academic health centres in Canada, and also connects practice-based research networks (MICYRN, 2013). MICYRN is coordinating several national initiatives to remove barriers and improve collaboration in clinical research, including:

- improving consistency and reducing duplication in ethics reviews;
- enhancing systematic analysis of resources for research, with templates and training; and
- sharing platforms and standards to increase pooling and comparability of data.

More information about each of these endeavours can be obtained from the MICYRN website (MICYRN, 2013). At the time of this assessment, these proposals were preliminary and not yet fully implemented or evaluated.

7 The Tri-Council Policy Statement, which guides the conduct of research supported by the Canadian federal granting councils, requires clinical trials be registered in a public registry before recruitment begins (Tri-Council, 2010). Other implications from this overarching research policy are elaborated later in the report. Also, in order to be considered for publication in biomedical journals, a protocol must be registered in a public registry (ICMJE, 2013), although a recent review suggests trial registration may nonetheless be inadequate or lacking completely in a majority of published clinical trials (Mathieu *et al.*, 2009).

Other initiatives are enhancing support for clinical trial activity more generally. In 2011, a National Clinical Trial Summit, sponsored by the Association of Canadian Academic Healthcare Organizations, the CIHR, and Canada's Research-Based Pharmaceutical Companies (Rx&D), brought together representatives from academic and industry-based research as well as government and related organizations (Rx&D *et al.*, 2012). Through the resulting Action Plan, participants issued nine recommendations for improving the atmosphere for clinical trial research in Canada. Since the summit, the sponsors have made progress on implementing some components of the recommendations and on planning for others. At this stage, this effort is entirely focused on research with adult participants. In the action plan and recommendations, as well as in the updates, research with children is notably absent. However, in the elaboration of the existing support for trial research, MICYRN's progress in harmonizing ethics review is identified as a model for collaborative processes (Martz *et al.*, 2012). Along with the ongoing work of the Standing Senate Committee on Social Affairs, Science and Technology (discussed in Chapter 1), the collaboration of the organizations sponsoring the summit is contributing to the environment for clinical trials in Canada.

Although these efforts are preliminary and their implementation or impact cannot be evaluated, the Panel noted they represent opportunities to improve the environment for pediatric trials, which remain the most highly sought source of evidence on the safety and effectiveness of medicines.

2.3 RESPONDING TO THE NEED FOR RESEARCH

The magnitude of off-label use reveals a lot about the demand for pediatric medicines research. As noted above, the research community has identified and is working to develop infrastructural and procedural supports that address some of the barriers to this research. However, an essential nuance is that Canada is not absent in all research activity, but rather is active in clinical trial research. According to analysis by MICYRN of data from the WHO portal, Canada is home to more clinical trial sites per capita than the United Kingdom and the United States. The Panel observed from this level of activity that preparedness for research is evident in Canada, but is not being fully engaged in support of the regulatory process. Clinical trial readiness is necessary but not sufficient for evidence to result in approval of new medicines, so the countries participating in research may not always benefit from the results of those trials through subsequent authorization of the medicine for use in children. As described in the case of Celecoxib (see Box 2.3), the clinical trial to evaluate its safety and efficacy included a Canadian study site, and therefore involved Canadian

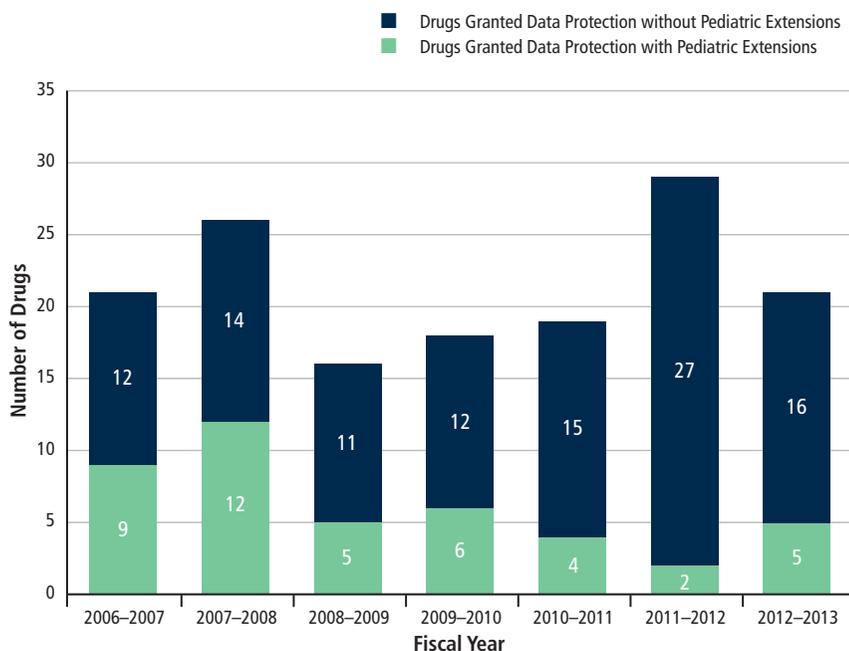
children, but did not result in the drug being labelled as safe and effective for use in children in Canada (Pfizer, 2008). Therefore, use of Celebrex® by pediatric patients in Canada remains off-label.

As mentioned earlier, under current legislation Health Canada does not require research and submission of data in support of an indication for use in pediatric populations, but it does provide incentives to encourage research on pediatric indications. A manufacturer of an innovative⁸ drug is awarded eight years of data protection, during which no one else may rely on or use the manufacturer's data to obtain market authorization for the same or a similar product, such as a generic⁹ version of the drug. When a manufacturer also provides results of clinical trials that were designed to increase knowledge about safety and efficacy of the medicine for pediatric use, the data protection is extended an additional six months (HC, 2011c). The pediatric information provided does not have to support a new pediatric indication but could confirm a contraindication or a warning against pediatric use. The knowledge from pediatric studies is then publicly available through a change to the label or the product monograph. In this way, both positive and negative trial results can contribute to the evidence about safety and effectiveness in children.

Since the data protection provision was introduced in Canada in 2006, 43 drugs have been introduced with the six-month extension for including information on pediatric use (OPML, 2013; HC, 2014a). However, as shown in Figure 2.3, the number of drugs approved without the pediatric extension has remained consistently greater than the number of medicines approved with evidence on pediatric use. In their review of drug investigation plans, the Paediatric Committee of the EMA found that 30% of medicines under study were not relevant, or possibly unsafe, for use in children (EMA, 2012e). The Panel's interpretation of this finding is that as many as two-thirds of drugs could be expected to have a pediatric indication.

8 An *innovative drug* contains a medicinal ingredient that has not previously been approved for use in Canada in a drug, for any indication (HC, 2011c).

9 A *generic drug* contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but does not necessarily contain the same non-medicinal ingredients as the brand name product (GoC, 2013).



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Figure 2.3

Drugs Receiving Data Protection in Canada, by Fiscal Year

Since the introduction of the extension to data protection for manufacturers submitting data pertaining to safety or effectiveness in children, only a minority of innovative drugs approved by Health Canada and granted data protection have included pediatric data. International examples suggest that as many as two-thirds of drugs could be expected to have a pediatric indication (EMA, 2012e). This figure reflects the activity level in granting pediatric extensions in Canada during the seven years following the introduction of this incentive. It was not possible to determine the number of products for which pediatric data were not submitted to Health Canada, even though the products were eligible for the extension. As Health Canada provides a five-year window after initial market approval (for an adult indication) for a manufacturer to file a supplemental application for this extension, drugs approved from 2009 onward may still have an extension filed.

In addition to the extension for information on pediatric use, Health Canada has several provisions for accelerating and simplifying the approval process, designed to support research on priority issues. Although not specific to pediatric studies, these have the potential to be applied to pediatric research within their respective mandates.

- **Priority Review:** For promising therapies for life-threatening or severely debilitating conditions, for which no similar product is currently marketed or the submission significantly improves on existing therapies (i.e., provides an increase in efficacy or decrease in risk of harm). Submissions must include the same information as other applications, but Health Canada commits to processing priority review submissions more quickly (HC, 2006). Priority review has been proposed as an incentive to manufacturers of pediatric medicines (HC, 2012f).
- **Generic Product Approval:** For products that contain the same amount of medicinal ingredient as an existing and previously approved product (HC, 2012b; Senate, 2012). Generic drugs do not require the same volume of evidence but can be approved on the evidence from Phase I bioavailability and clinical trials. A submission for a generic drug, eligible for approval after patent expiration and the data protection period on the original product, can be reviewed by Health Canada in an abbreviated application process (HC, 2013c).
- **Orphan Drugs:** For drugs intended for treatment of rare diseases, defined by Health Canada as life-threatening or seriously debilitating, or serious and chronic conditions that affect fewer than 1 in 2,000 people (HC, 2012a). Health Canada is currently developing an approach for encouraging this research. Because these conditions affect small numbers of people, the challenges in developing and marketing orphan drugs are compounded by a smaller economic benefit on a population basis. A proposed regulatory framework would designate orphan drugs as a gateway to incentives for the manufacturer and relax provisions for the regulator. Sponsors of orphan drug development would have access to scientific and clinical protocol advice from Health Canada as well as priority review of applications, and would be required to register all clinical trials and conduct monitoring following market authorization (HC, 2012a). Canada is also contributing to international efforts for building and sharing knowledge on rare diseases (IRDiRC, 2013; Orphanet, 2013).

The implication of these alternatives is that drug products can be authorized flexibly without sacrificing safety, efficacy, or quality when there is heightened need. The alternatives to the usual submission process include accelerated review of applications by Health Canada and, in the case of generic products, limited data requirements. To ensure children have timely access to medicines with robust evidence, these provisions could be used to encourage pediatric medicines research with eligible medicines and might also be adaptable to pediatric medicines more broadly.

2.3.1 International Experience in Pediatric Medicines

The recent regulatory and legislative initiatives for pediatric medicines research of the United States and the European Union have demonstrated that effective tools can be developed for improving the quality and quantity of pediatric medicines research and these experiences can provide insights relevant to Canada.

On the surface, some features of the United States and European Union systems are similar. Both offer financial incentives to encourage research on pediatric indications and have backed the incentive with the requirement to consider pediatric use in all drug applications as a condition of authorization (Boots *et al.*, 2007; Olski *et al.*, 2011; Hoppu *et al.*, 2012). In each case, the regulator controls some central functions, such as the ability to identify priorities for research and to advise on study design for children.

Food and Drug Administration

In the United States, the FDA is the federal agency responsible for drug approvals. The legislative initiatives stimulating pediatric medicines research in the United States were first enacted in 1997. While these initiatives have evolved in the past decade, they have continued to centre on incentives to conduct pediatric research. In broad terms, these incentives consist of the authority to require pediatric studies in particular circumstances and the ability to offer additional market exclusivity¹⁰ in return for the conduct and submission of requested pediatric studies.

Since their introduction in 1997 and 1998, respectively, these two provisions have been reauthorized in various forms.¹¹ In 2002, the exclusivity provision became part of the *Best Pharmaceuticals for Children Act* (BPCA), and the study requirement under the Pediatric Rule was replaced in 2003 with the *Pediatric Research Equity Act* (PREA). Reauthorized again in 2007, most recently both provisions were made permanent as part of the 2012 *FDA Safety and Innovation Act* (FDASIA) (U.S. Congress, 2012).

10 When granted by the FDA in exchange for submission of pediatric data, additional market exclusivity confers the exclusive right to sell the product, and all forms of the active molecule marketed by the applicant, across all ages for an additional six months following expiry of patent or other data protection.

11 The FDA established the first incentives for pediatric medicines research — the Pediatric Exclusivity Provision — in the *FDA Modernization Act* of 1997. The following year, through the Pediatric Rule, the FDA asserted the authority to require studies of pediatric populations in applications for new therapies and new indications (Frakking *et al.*, 2009).

Through various iterations, these provisions have stimulated pediatric medicines research. The BPCA offers financial incentives to conduct pediatric studies, where a therapeutic need exists, while products are covered by patent protection or other data exclusivity provisions. As part of this program, the pediatric exclusivity provision grants an additional six months of market exclusivity if a company sponsoring an application performs pediatric studies as requested by the FDA. In what is referred to as a written request, the FDA specifies the indication or indications to be investigated, the age ranges of interest, the formulations to be studied — and, if necessary, developed — as well as other requirements for study design¹² (Li *et al.*, 2007; Benjamin *et al.*, 2009). The written request may specify extension of the adult label, or of an adult off-label use, to children and may be invited by a sponsor (through an offer to the FDA) or initiated by the FDA or by the National Institutes of Health (NIH).

If a sponsor declines the written request, regardless of whether the product has any remaining patent protection, the FDA may refer the study to the NIH. Although the exclusivity provision encourages research on products still covered by patent protection, the BPCA thus also provides a mechanism to encourage research on off-patent products — products for which patent protection has ended. To this end, the NIH maintains a list of off-patent pediatric therapeutic priorities and can fund studies from this priority list, if a sponsor declines a written request (IOM, 2012b).

When it undertakes an investigation under PREA, a sponsor submits a Pediatric Study Plan (PSP) that outlines the intended studies, their objectives and design, age groups, relevant endpoints, statistical approach, and plans for development of pediatric formulations, according to the guidance provided by the FDA (FDA, 2013a). The sponsor submits the PSP to the FDA following the completion of Phase II studies in adults or before Phase III studies are initiated. The PSP is reviewed by the FDA's Pediatric Review Committee, which considers both the scientific and ethical issues in any study as well as consults on a wide range of other issues related to BPCA and PREA (IOM, 2012b). At this point, the sponsor also specifies any intention to request a waiver or deferral if they see reason to not study the drug in all pediatric populations, although such a request is not finalized until marketing authorization and may be adjusted by the sponsor, with agreement of the FDA, in the interim. A sponsor can request a waiver of the requirement to study pediatric populations if:

12 A written request also specifies non-clinical studies (if applicable), study design(s) and objective(s), inclusion and exclusion criteria, study end points, and statistical considerations (including sample size). The required studies vary in design depending on the existing knowledge and the purposes of the investigation. Not all required studies are clinical trials of safety and efficacy (Dunne *et al.*, 2011).

- The drug does not represent a meaningful therapeutic benefit over existing pediatric therapies.
- The drug is unlikely to be used by a substantial number of pediatric patients.
- Necessary studies would be impossible or highly impracticable.
- Evidence suggests the drug would be ineffective or unsafe in all pediatric age groups; this information must be included in labelling.

(IOM, 2012b)

A partial waiver, which precludes the need to study specific pediatric age group(s), may be granted if any of the above criteria apply for that particular age group, or if the sponsor can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. In such cases, an explanation of why a formulation cannot be produced must be publicly available on the FDA website. This provision for waivers has been used only once at the time of writing (S. Nelson, personal communication, 2013).

The initial PSP should also include any plans to request deferral of pediatric studies in some or all pediatric groups. The FDA may grant a deferral of required pediatric studies if:

- The drug or biological product is ready for approval for use in adults before pediatric studies have been completed.
- Pediatric studies should be delayed until additional safety or effectiveness data have been collected in adults.
- There is another appropriate reason for deferral.

(IOM, 2012b)

If deferred, pediatric studies are still required, but are conducted or completed following approval of an adult indication. Post-marketing requirements can also include further pediatric study if the initial application did not cover all ages or indications. The results of these post-marketing studies can change the authorization for the medicine. In that case, the FDA requires that product labels be changed not only to incorporate new pediatric indications or dosing information but also to include study results that find safety or efficacy concerns in pediatric populations (Benjamin *et al.*, 2009; IOM, 2012b).

When pediatric investigations are completed, a sponsor submits the results of the clinical studies and any necessary labelling changes along with the application for marketing. This submission, known as a pediatric assessment, contains the data to determine the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations. The assessment is based on an appropriate formulation for each age group and supports dosing and administration for each age group (FDA, 2005b).

Under BPCA, market exclusivity extension is granted if study methods, results, and reporting meet the conditions of the written request, regardless of the findings (GAO, 2007, 2011). Because the extension of market exclusivity applies to all forms of a drug that contain the same active ingredient, the financial benefit to the sponsor from the exclusivity provision is greater for drugs that have high profit margins in adult use (IOM, 2012b). By contrast, under the PREA, the FDA can require that a pediatric assessment be included in marketing applications, without granting additional exclusivity, for a drug that includes a new active ingredient, new indication, new dosage form or regimen, or new route of administration, if that new product, indication, and administration are appropriate for children (FDA, 1999; FDA PeRC, 2010).

The evolution of United States legislation has provided opportunities to clarify and expand the expectations and has, ultimately, resulted in more pediatric studies and more label information for children's use of drugs and biologics. In the first 16 years of the exclusivity provision (1997–2013), market exclusivity was granted for 199 products (FDA, 2014a) and further study resulted in 500 changes to label information (FDA, 2013b). The peak year for written requests was 1999; although the volume of requests has decreased since then, the FDA has used the requirement in the PREA more frequently (IOM, 2012b).

The United States Government Accountability Office (GAO) has investigated the implementation of the pediatric medicines legislation. Based on a four-year sample of studies motivated by the pediatric exclusivity provision, the GAO found that a majority of the sponsors of on-patent products agreed to written requests for pediatric studies from the FDA (GAO, 2007). Retrospective data show that the majority of written requests were actually initiated by the sponsor — although then issued by the FDA — and an estimated 10% of submissions have actually been based on reanalysis of existing data rather than new studies (IOM, 2012b). Other evaluations of the legislation's impact have come from more focused studies. A recent investigation by Laughon *et al.* (2014) suggests that newborns may not benefit from the label changes to the same extent as other pediatric subgroups. In other studies, the cost of pediatric studies requested by the FDA has been demonstrated to vary substantially, depending in part on the type of trial required (Li *et al.*, 2007). In almost all cases, research into pediatric use of on-patent medicines resulted in a net economic benefit for a sponsor (Li *et al.*, 2007; Baker-Smith *et al.*, 2008). For off-patent products, however, the majority of requests were declined by sponsors (GAO, 2007). As off-patent products are not eligible for market exclusivity, funding from the NIH as part of BPCA is intended to enable pediatric studies.

Impact of Pediatric Medicines Research in the United States

The Institute of Medicine convened a committee to examine the BPCA and the PREA. In its 2012 report, the committee identified several aspects of the policy framework that could be strengthened. Some suggestions have been addressed in the 2012 Act, and others could be considered in future improvements:

- improved clarity in FDA reviews concerning rationale for use of alternative endpoints and extrapolation, justification for placebo-controlled trial design, and anticipated health benefit;
- increased use of long-term post-market follow-up studies;
- strengthened study designs in PSPs; and
- wider dissemination of FDA review findings — for example, on PubMed or trial registries — to address reporting that has lagged behind expectations.

(IOM, 2012b)

The FDA *Safety and Innovation Act*, passed in 2012, addresses some areas identified for improvement in previous reviews. The new Act:

- elevates the importance of neonatal studies by requiring a rationale for the exclusion of neonates from written requests;
- enhances the FDA's ability to review PSPs and assessments by adding staff with expertise in neonatology;
- requires posting on the FDA website of complete information from medical, statistical, and clinical pharmacology reviews for products granted pediatric exclusivity and a change in product labelling between 2002 and 2007;¹³ and
- allows the FDA authority to penalize sponsors for not submitting agreed pediatric study results.

(U.S. Congress, 2012)

These provisions are too recent to evaluate. However, the Act introduces a five-year evaluation of implementation, and specifies indicators for reporting, to be provided to the government and made publicly available.

13 BPCA required the posting of summaries. In 2007, the *Food and Drug Administration Amendments Act* (FDAAA) required the posting of the actual reviews (prospectively) for both PREA and BPCA. FDASIA extended the posting of the full reviews retrospectively to cover the BPCA products submitted between 2002 and 2007 (U.S. Congress, 2012).

European Medicines Agency

The EMA coordinates the system regulating and monitoring medicines for the member states of the European Union (EMA, 2014b). Within this system, medicines can be authorized centrally — by the European Commission, informed by scientific opinions from the EMA — or through a decentralized procedure or a mutual recognition of national authorization procedures by individual countries. For some designated categories, medicines must be authorized centrally. The EMA is the sole provider of scientific opinions on orphan designation and advanced therapies medicinal products classification. It is the referral centre in case of disagreement between member states. At other stages in the medicines development process (e.g., authorization of clinical trials for medicines, pricing, reimbursement, and patent protection), the responsibility is purely national. Some other activities — such as scientific advice on development and pharmacovigilance — can be managed either centrally or nationally (EMA, 2014a, 2014b).

Support for pediatric medicine research was included in the *Paediatric Regulation*, which took effect in 2007 and listed new responsibilities both for the sponsors of new products and for the regulator (Olski *et al.*, 2011). This regulation introduced the requirement for every application for a medicine to consider the potential pediatric use of the product. The sponsor must propose and agree to a development plan, known as the Paediatric Investigation Plan (PIP), which is submitted following adult pharmacokinetic studies (Olski *et al.*, 2011). This document specifies pharmaceutical, non-clinical, and clinical studies to establish efficacy, safety, and quality in newborns, infants, children, and youth. The PIP further specifies the timing of pediatric investigations relative to adult studies and details the measures for adapting the form and formulation for pediatric populations as well as clinical trial design, inclusion criteria, endpoints, study duration, and comparators (Olski *et al.*, 2011; EMA, 2012e, 2014c).

The Paediatric Committee (PDCO)¹⁴ evaluates each PIP and provides an opinion to the applicant: a waiver, a deferral, an approval of the proposed or modified PIP, or a negative opinion. The opinion is followed by a binding decision from the EMA (Olski *et al.*, 2011). At the submission of a PIP, the PDCO can waive the requirement to study particular pediatric age groups or children altogether if the condition in question does not affect pediatric populations or if the product is likely to be ineffective, unsafe, or lacking benefit over existing therapies. Evidence from the first five years indicates that pediatric data were required for the majority of applications. Before the *Paediatric Regulation* came into effect, only 30% of medicines were approved for a pediatric indication.

14 The Paediatric Committee comprises delegates from 28 European Union member states, Norway, and Iceland as well as health professionals and representatives of patients' associations (Olski *et al.*, 2011; A. Saint-Raymond, personal communication, 2014).

In contrast, in 2011, 30% of PIPs were granted a full waiver, so the other 70% of PDCO opinions recommended research with pediatric populations (EMA, 2012e). This suggests that the requirements introduced through the *Paediatric Regulation* have more than doubled the proportion of applications for new medicines that will be accompanied by pediatric data.

The PDCO can also defer pediatric research “so as not to delay the marketing authorisation in adults and to perform studies in children when it is safe to do so” (EMA, 2012e). In the first three years of the *Paediatric Regulation*, 82% of pediatric trials were deferred until after approval for an adult product, and the average delay was three to five years after the submission of the PIP (Olski *et al.*, 2011).

In many cases, the PDCO requests modifications to the proposed PIP (Olski *et al.*, 2011). The modifications vary. Examples include:

- encouraging extrapolation of efficacy from trials with adults, so fewer children are required to participate (EMA, 2012e) (see also Chapter 5);
- requesting additional research to address known concerns related to forms and formulations, such as the safety of excipients and palatability (EMA, 2012e) (see also Chapter 4);
- requesting study in additional age groups, such as extending participation to newborns (Olski *et al.*, 2011); and
- increasing or decreasing the number of patients required in trials (Olski *et al.*, 2011).

Through approval of the PIP, the regulator can influence studies for new products. Furthermore, medicines already marketed to the public and still covered under patent are subject to the *Paediatric Regulation* when a request for a new indication, new route of administration, or new pharmaceutical form is submitted (Olski *et al.*, 2011). As with extension provisions in Canada and the United States, under the *Paediatric Regulation* the reward for completing all studies in compliance with the agreed PIP, regardless of the findings, is an extension of the patent by six months (EMA, 2012e). However, the patent can be extended only once, although the PIP obligations may be repeated if the product is submitted for new indications or conditions, forms, or routes of administration (Olski *et al.*, 2011). The *Paediatric Regulation* also provides an incentive to extend the knowledge about priority off-patent products already on the market. The PDCO maintains a list of off-patent pediatric medicines that are priorities for study, and the European Commission has provided funding for research on some of these treatments (EMA, 2012e). In addition, a manufacturer that develops pediatric forms of medicines previously approved for marketing to adults may be granted 10 years of data protection and market exclusivity through a Paediatric Use Marketing Authorization (PUMA) (EMA, 2012e).

Impact of the *Paediatric Regulation*

A five-year evaluation of the *Paediatric Regulation* (EMA, 2012e) showed that it had stimulated the authorization of medicines with an initial pediatric indication, directly resulting in 30 new pediatric indications. Subsequent follow-up has attributed 15 new pharmaceutical forms adapted for children, and 387 additional labelling changes based on pediatric trials and studies (EMA, 2013c). However, the evaluation found that the PUMA provision was under-used, pointing to the challenges with existing products authorized for use in adults but used extensively off-label in children. As well, the evaluation found that the data protection provisions may not provide enough incentive for off-patent medicines, in particular their pediatric form (EMA, 2012e).

The PIP provides an opportunity for the regulator to integrate pediatric needs in the development of viable products. The five-year evaluation noted the current intended timing of the PIP submission is often delayed compared to adult development timelines, as many manufacturers submit the PIP after the deadline. Since the PIP submission is intended to inform study design, delays may represent a “missed opportunity for early regulatory dialogue” (EMA, 2012e).

The *Paediatric Regulation* also provided transparency measures by mandating the submission of older pediatric studies (pre-dating 2007) for publication in a European Union database of clinical trials, thus providing a searchable public gateway to protocol- and results-related information (European Parliament & Council of the European Union, 2006).¹⁵ Similarly, the Regulation obliges manufacturers to report to regulators on any pediatric trial for an approved product within six months of its completion. In addition, any pediatric trial must be recorded in the European Union database of clinical trials, along with results (European Parliament & Council of the European Union, 2006).

This evidence suggests that, since the *Paediatric Regulation* took effect, knowledge about pediatric medicines continues to build. The *Paediatric Regulation* altered the landscape for drug studies for children in the European Union, with implications for current and future studies as well as for existing medicines. As a result of the changes, evidence on pediatric medicines use is accumulating both from PIPs for new products and from deferred studies from previous PIPs.

15 This database lists about 3,000 study reports, and another 3,000 study reports have been submitted to the database but are not yet available. The total number of older studies is about 20,000, corresponding to 1,200 active substances — the active pharmaceutical ingredients of drugs. The website of the clinical trial database is <http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/index.php>.

2.3.2 The Canadian Experience and Lessons for Canada

Since the United States passed legislation to improve the available evidence for use of innovative medicines in children, Canada has provided only a single financial incentive under data protection regulations, one with limited success in stimulating pediatric medicines research. Canada has not followed either the United States or the European Union in legislating requirements to enhance the safe and effective use of medicines in children. Furthermore, there appears to be a substantial gap in the submission of existing pediatric trial data to the Canadian regulator. As shown in Figure 2.3, since 2006, when the data protection extension was enacted, only 43 new drug submissions to Health Canada were accompanied by sufficient pediatric data to grant the data protection extension. In contrast, and in response to an alternative approach for regulating medicines research, several hundred applications in the United States have been approved for labelling changes that increase pediatric indications, resulting in many medicines approved for pediatric use elsewhere but not in Canada.

Globally, the conditions that affect children most are not the ones studied most in medicines research (Bourgeois *et al.*, 2014). Financial incentives to study pediatric populations may not be enough to motivate applications for pediatric indications. Further, the drugs studied under pediatric extension provisions may not be the ones most needed by children (Boots *et al.*, 2007; Hoppu *et al.*, 2012). Thus, other jurisdictions have combined incentives with requirements to consider pediatric use in all medicines applications as a condition of authorization. In the European Union, the impetus for pediatric medicines research was established with a single regulation, while the United States model involved incremental change to legislation. Through these policy reforms, the regulators now have the authority to require study of pediatric populations. Both the FDA and the EMA require consolidated pediatric-specific documents, subject to expert advice, to improve the quality of the research. The regulators have also centralized authority over priorities for pediatric medicines research.

In both the United States and the European Union, regulation and legislation have measurably increased both the quantity and quality of research on medicines for children. The regulatory requirement and the financial support may not, in sum, be sufficient either; research is fostered by strong infrastructure that encourages and enables the complex activity involved in drug studies.

Pediatric research is enabled through incentives and supports that change the opportunities for manufacturers. Among the supporting infrastructure:

- Clinical trials databases in both the United States and the European Union are intended to improve the transparency of the extent, nature, and results of ongoing research; to reduce duplication in research effort; reduce selective outcome reporting bias; and to track trends in research (EMA, 2012e; Field *et al.*, 2013).
- Both the United States and European Union have established a list of priorities for pediatric medicines research (EMA, 2012e; IOM, 2012b) to guide the activities of researchers and regulators in their jurisdiction.
- Medicines regulators already collaborate to optimize the use of resources for medicines research:
 - Monthly meetings of a Pediatric Cluster, consisting of representatives from the FDA, EMA, Health Canada, and the Japanese medicines regulator (Saint-Raymond, 2013) provide the opportunity to discuss the specific products submitted to the FDA and EMA. The cluster deliberates on many issues, including those related to ethics, study design, and safety and, through the discussions, agrees on a common approach to be communicated to the sponsor.
 - Regulators have also developed disease-specific collaborations. For example, through the international Inflammatory Bowel Disease Working Group, representatives from the same regulatory agencies collaborate to increase the consistency on expectations for clinical trials. In monthly teleconferences, the working group discusses standards for scientific and ethically appropriate study designs and approaches for evaluating outcomes, with the goal of harmonizing internationally accepted measures (Sun *et al.*, 2014).
- Research networks have been formed to connect expertise, identify efficiencies and gaps, support ongoing research infrastructure, and reduce duplication:
 - The European Network of Paediatric Research at the EMA (Enpr-EMA) is a virtual collaboration of national and European networks specializing in studies in pediatric populations (EMA, 2012e). The Enpr-EMA has established quality criteria for standards in a research network. Canada's MICYRN (see Section 2.2) is a member of Enpr-EMA and is represented on the coordinating group.
 - The U.S. Pediatric Trials Network (PTN) is a multi-institutional network with the primary objective of providing effective infrastructure for the ethical conduct of pediatric clinical trials, including pharmacokinetic, safety, and efficacy studies, for submission to the FDA (IOM, 2012b; PTN, 2014).
 - See Chapter 5 for other examples of initiatives (e.g., the Medicines for Children Research Network, the Pediatric Rheumatology International Trials Organization) that are increasing consistency across trials and improving the match between trials and regulatory standards.

- Scientific advice and regulatory assistance are provided by the committees for pediatric review and approval attached to the FDA and EMA (FDA PeRC, 2010; EMA, 2012e). In PIP opinions, the PDCO highlights opportunities for orphan designation of particular medicines or conditions, and also engages discussions with the orphan medicines development program, recognizing the synergy between orphan medicines and pediatric research (EMA, 2012e).

The Panel sees an opportunity for Canadian lawmakers to remedy the disparity in authorization of drugs for pediatric use and address the frequent off-label prescribing of pediatric medicines in Canada. While the return on financial incentives offered in the United States or European Union likely cannot be realized in Canada, the incentive under data protection regulations could offset a new regulatory requirement for the submission of existing data, previously submitted in other jurisdictions, to Canadian regulators.

As evidenced by the different approaches to pediatric medicines research in the United States and European Union, no one formula will suit all situations. Canada is unique and requires a custom-fit model, appropriate to the size of the market for medicines and the influence of regulatory decisions from other jurisdictions. The shape and size of incentives may not match exactly the arrangements from the United States or European Union, but may be suited to the available resources and anticipated responses. Decisions that influence patient access to medicines are made both federally and provincially. Nonetheless, the experiences of international counterparts can offer insight into opportunities for Canada's federal policy framework. In addition to benefitting from the experience of each jurisdiction in encouraging pediatric medicines research, Canada might also observe opportunities to harmonize with effective international policies.

Canada has explored this direction before. Bill C-51, *An Act to Amend the Food and Drugs Act*, was introduced in 2008, but did not become law before the session of Parliament ended (Tiedemann, 2008). At the time of the Panel's deliberations, a new proposed amendment to the *Food and Drugs Act* with similar provisions was before the government, in Bill C-17. The proposed amendments would change the authority granted to the federal regulator. For example, it would empower Health Canada to recall drugs, require manufacturers to provide any information within their control, require changes to product labels, and impose enforcement for non-compliance (House of Commons, 2013). Although observers have noted opportunities to broaden Health Canada's regulatory mandate even further, for example, with mandatory clinical trial registration and release of study results (Herder *et al.*, 2014) and with post-approval pediatric specific safety reviews (Senate, 2014), this expanded mandate might bring Canada's regulatory framework in line with those of other international regulators in obtaining the evidence needed for pediatric indications.

2.4 CHAPTER SUMMARY

Each year, about half of Canada's roughly seven million children are prescribed at least one medication. However, proportionally few medicines are approved for use in infants, children, and youth. As a result of the scarce information on safe and effective medicines, off-label use of medicines among pediatric patients is common. Although children benefit from these medicines for a wide range of conditions, they face possible harms when taking a drug that is not proven to be safe and effective for their use.

This situation arises from the current regulatory framework for pediatric drug approval in Canada. Health Canada oversees the development of safe and effective medicines and offers various supports for research, including standards and incentives for research on priority issues. Health Canada does not currently have the authority to require manufacturers to submit data on pediatric use of medicines. However, manufacturers are encouraged to study the safety and effectiveness of drugs in children and then submit this information. Despite this encouragement, the product label and prescribing information often reflect that the pediatric use of a medicine is not supported with evidence. In turn, prescribers' decisions about the use of medicines rely on a range of information sources, not all of which meet standards for rigorous evidence.

The current regulatory incentive to submit information on pediatric medicines may be insufficient motivation for manufacturers to conduct additional research. Research into the development of drugs for children is required, encouraged, and monitored with different, but effective, obligations and incentives in both the United States and the European Union. The success of international initiatives may also be attributable to other contextual features. For instance, research is fostered by an environment and by infrastructure that encourages and enables the complex activity involved in drug studies. This might include collective priorities for pediatric medicines research, alongside platforms and portals that allow sharing of information about trials, findings, and results. In combination, these features might improve communication about the coherence of the overall research effort. Interactions that improve the match between the sponsor's submission and the regulator's evidence needs, such as through mandatory review phases that include scientific advice, could contribute to a greater return on the research effort, as measured in authorized medicines. Supportive infrastructure for furthering pediatric medicines research might also include networks that foster research capacity, by facilitating multi-centre trials, by addressing the challenges to research, and by shifting to a more research-based culture.

3

Children Are Not Small Adults: Considering Variation in Drug Response

- **Variability in Drug Response in Children**
- **Pharmacokinetics and Human Development**
- **Pharmacodynamics and Human Development**
- **Pharmacogenomics and Pharmacogenetics in the Developing Child**
- **Approaches to Investigate Pharmacokinetics and Pharmacodynamics in Children**
- **Addressing Knowledge Gaps**
- **Chapter Summary**

3 Children Are Not Small Adults: Considering Variation in Drug Response

Key Findings

- As children grow, they experience significant developmental changes that impact how their bodies deal with medications and how medications in turn affect their bodies. The most dramatic age-related physiological changes occur during the first year of life.
- These changes translate into variable drug responses among different stages of development (e.g., a newborn reacts differently from a child) and variable responses between children and adults; developmental changes must therefore be taken into account to ensure effectiveness and safety of treatment for children.
- Generally speaking, pre-term newborns, term newborns, and young infants have immature metabolism and excretion and thus need a lower dose of medication than adults; toddlers and children have faster drug clearance (normalized for body weight) and need a relatively higher weight-based dose than adults to avoid therapeutic failure; and adult information is usually more easily transferable to adolescents. Each of these dosing strategies can be greatly affected by other factors during different stages of growth and maturation.
- How children respond to a drug is greatly affected by genetic variations among individuals and among groups. Given the rapid increase in the discovery of genetic variations potentially underlying variability in drug response, the field of pharmacogenomics holds promise for explaining and predicting differences in drug efficacy and adverse responses among individuals.
- To fill knowledge gaps, pediatric drug research can take advantage of new methods, such as modelling and simulation and alternative sample collection techniques, to maximize safety and minimize distress in participating children.
- Despite emerging developments, there is still a general lack of pharmacokinetic, pharmacodynamic, and pharmacogenomic information related to children, particularly in newborns and young infants.

3.1 VARIABILITY IN DRUG RESPONSE IN CHILDREN

As children grow, they undergo significant developmental changes that impact how their bodies deal with medications (pharmacokinetics) and how medications, in turn, affect their bodies (pharmacodynamics). These changes render a child's response to medications different from that of an adult and can also translate into variable drug response at different stages of development (e.g., the response

of a newborn will differ from that of a child). Responses can also vary due to a number of factors unrelated to age and development that can affect both pharmacokinetics and pharmacodynamics. These include genetic make-up, sex, concurrent therapies, type of dysfunction or disease state, diet, environment, physical or mental health, and many others. Thus, the same dose of a drug may or may not be effective — or even toxic — depending on developmental and individual factors. Figure 3.1 provides a framework for these factors, describing how variations in pharmacokinetic and pharmacodynamic processes interact to affect the clinical response to a drug and highlighting the host of factors that determine the overall variability in drug response between individuals. To ensure effective and high-quality care options, and to avoid adverse events, these factors should be considered in combination when developing drug treatment for children and when prescribing and administering medications to this population.

This chapter provides an overview of the developmental factors responsible for the variability in drug response between children and adults as well as between different pediatric age groups. It also addresses how underlying genetic make-up contributes to this variability and how pharmacogenomic data need to be interpreted in the context of growth and maturation. Furthermore, the chapter considers how this information might inform future clinical pharmacological study. Other modifying factors (e.g., disease state, diet, environment) highlighted in Figure 3.1 are beyond the scope of this report. The chapter focuses primarily on review literature, which presents clear evidence why research involving children is essential to developing medicines for this population. Pediatric issues regarding forms and formulations are discussed in Chapter 4. Challenges in carrying out research in children are addressed more specifically in Chapters 5 and 6.

Because of how relevant developmental changes are to health and drug response, the ICH has established terminology for the age groups generally corresponding to stages of development (see Figure 3.2) (ICH, 2000a). These developmental stages are used as a reference point for this chapter to explain differences among children, although the variability seen in drug disposition, receptors, and signalling mechanisms related to human development may not correspond exactly to these defined age groups. Ultimately, this chapter uses these stages to demonstrate that ongoing developmental changes, combined with genetic and other individual factors, make the task of developing evidence-based dosing guidelines in children challenging, and that these stages must be considered in drug development studies.

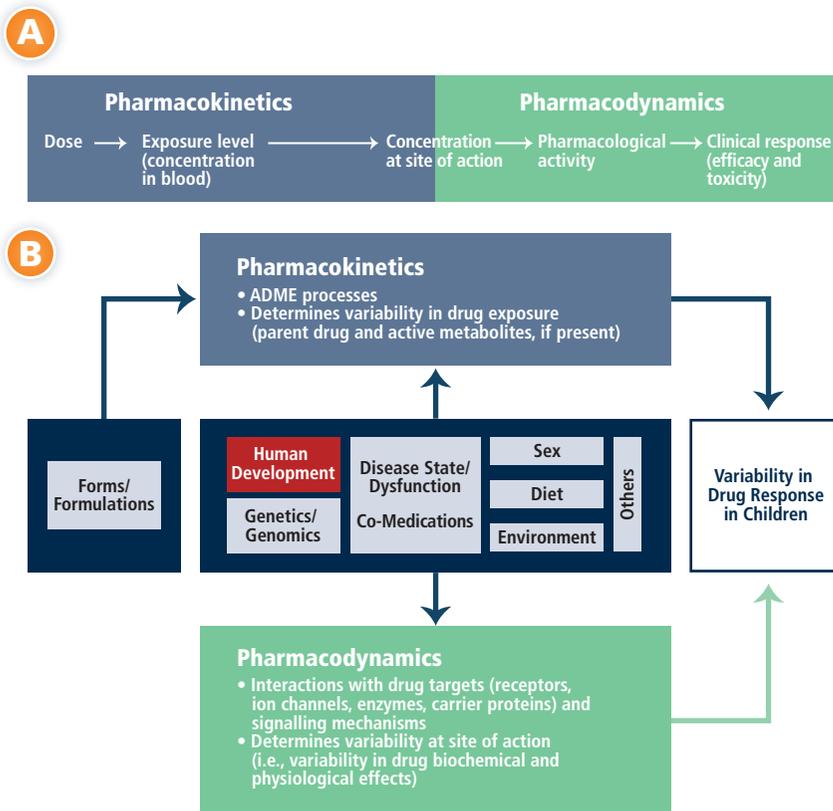
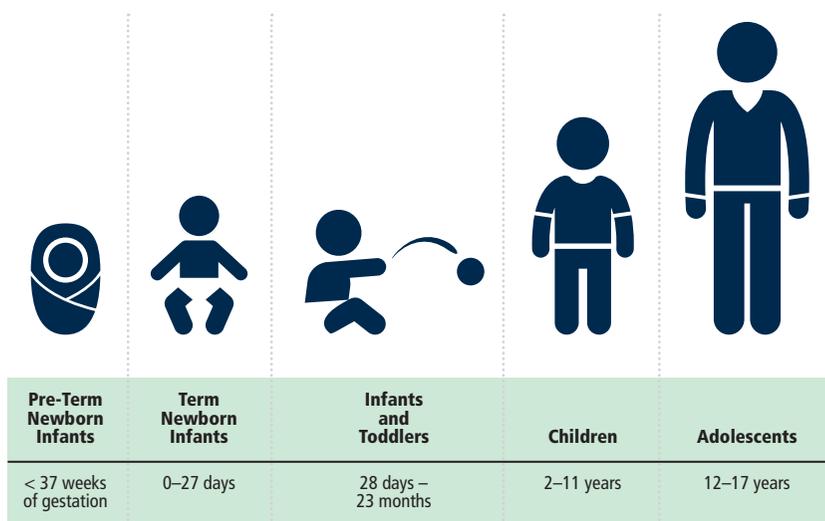


Figure 3.1

Factors that Affect Overall Variability in Drug Response in Children

(A) The level of exposure (i.e., the concentration of the drug in the systemic circulation) is dictated by pharmacokinetic processes — absorption, distribution, metabolism, and excretion. Based on the exposure level, pharmacodynamic processes, such as interaction of drugs with receptors, affect the activity of the drug at the site of action. (B) Overall variability in drug response in children is determined by pharmacokinetic and pharmacodynamic processes, both of which are affected by developmental changes and numerous patient-specific factors including genetic variations (discussed in Chapter 3). The form or formulation of a drug impacts the degree to which children will accept it (e.g., adherence) and can affect its bioavailability (discussed in Chapter 4). Other modifying factors (e.g., disease state, diet, environment), although noted in this figure, are beyond the scope of this report.



Data Source: ICH (2000a)

Figure 3.2

The Five Stages of Human Development

The ICH has established a range of categories that mark the stages of human development: pre-term newborn (<37 weeks gestation); term newborn (0 to 27 days); infants and toddlers (28 days to 23 months); children (2 to 11 years); and adolescents (12 to 16 or 18 years, depending on region) (ICH, 2000a). These stages help to distinguish differences among groups of children.

3.2 PHARMACOKINETICS AND HUMAN DEVELOPMENT

Pharmacokinetics is the term for the physiological processes affecting administered drugs. These processes include absorption, distribution, metabolism, and excretion, collectively referred to as *ADME* (Van den Anker *et al.*, 2011). *ADME* processes, which determine the resulting concentration of a medication in the systemic circulation, are affected by major physiological changes that occur in developing children. Children are more likely to receive medications orally than any other administration route (excluding vaccines) (Rakhmanina & van den Anker, 2006), and orally administered drugs are subjected to more complex *ADME* processing than other drugs (e.g., those administered intravenously). Each of the *ADME* processes and their relation to human development are described in greater detail in this chapter. Table 3.1 summarizes the changes in these specific pharmacokinetic processes for each of the developmental stages and describes their implications for drug efficacy and safety. This information forms the basis for practice guidelines for clinicians to determine appropriate doses and for researchers to develop safe and effective medications for children at different developmental stages.

3.2.1 Absorption

The absorption of a drug describes its movement from the site where it is administered to the bloodstream (systemic circulation), including the rate at (and the extent to) which this occurs. It is from the bloodstream that the drug will reach its site of action.

Absorption depends on the route of administration to the body (e.g., oral administration, rectal administration), the physiology of the individual (e.g., the rate of intestinal and hepatic metabolism), and the physiochemical characteristics of the drug (e.g., molecular weight, solubility, degree of ionization) (Johnson, 2011). Absorption plays a significant role in determining *bioavailability*—the percentage of a dose that reaches the systemic circulation in unchanged form (Holford, 2009).

Medications administered intravenously immediately enter the bloodstream and usually have 100% bioavailability. However, medications that are administered through extravascular routes, such as enteral (oral and rectal), percutaneous (topical), intramuscular (injection), subcutaneous (injection), or intrapulmonary (inhaled), must overcome numerous chemical, physical, mechanical, and biological barriers to reach the systemic circulation (Tayman *et al.*, 2011). Different routes offer different challenges and benefits, depending on the developmental stage of the child, and can vary depending on genetic differences. A description of both the routes of administration and the parameters that must be considered to determine the appropriateness of each route is provided in the following discussion. The specific parameters mentioned (e.g., gastric emptying, skin thickness) were identified as the most relevant for a discussion of developmental changes that affect drug absorption. Other processes, such as nutritional status,¹⁶ the presence of disease, or genetic differences, can cause additional variability in drug absorption. Information on how a medication will be absorbed is necessary to make appropriate choices about the type of medication and the appropriate dose for individuals at different stages of development.

Enteral Absorption Following Oral Administration

Oral administration of drugs is the most common route of delivery for pediatrics (excluding vaccines). Changes in stomach pH throughout development can affect the stability and the degree of ionization of drugs, which in turn, affect the amount of drug available for absorption (Kearns *et al.*, 2003). In newborns and very young infants, the solubility of lipophilic drugs, such as fat-soluble vitamins, is reduced as a consequence of low production of bile salts, and results in diminished absorption (Johnson, 2011). Delayed gastric emptying (rate

¹⁶ Diet varies considerably during childhood (from breastmilk and infant formula to puréed food to adult diet), and very little is known about the impact of a child's diet on drug absorption.

of removal of a drug from the stomach) in newborns and young infants can delay absorption of drugs, since most drugs are absorbed in the small intestine (Strolin Benedetti & Baltes, 2003; Johnson, 2011). Young children have a short intestinal transit time, resulting in inefficient absorption of some sustained release products (Bartelink *et al.*, 2006). Following absorption, medications administered orally are subjected to the *first pass effect* — the metabolism of drugs by gastrointestinal and hepatic enzymes, as well as the effect of intestinal drug transporters, which can alter the concentration of unchanged drug that reaches the systemic circulation (Johnson, 2011). Intestinal CYP3A4 and P-glycoprotein (discussed in Sections 3.2.3 and 3.2.5, respectively) are key players in limiting drug absorption at the level of the enterocyte. Intestinal CYP3A4 activity is significantly lower in newborns compared to children older than 12 years (Johnson *et al.*, 2001). Altered expression of drug-metabolizing enzymes and transporters can lead to an increase or decrease in bioavailability or activity of a drug. For example, a newborn may be less affected by first pass metabolism than an older child because of the immaturity of the gastrointestinal and liver enzymes, resulting in higher bioavailability in newborns (Johnson & Thomson, 2008; Johnson, 2011).

Enteral Absorption Following Rectal Administration

The rectal route can be useful when oral ingestion is not possible (e.g., when a child is vomiting). Because rectally administered drugs are subjected to hepatic first-pass metabolism, the bioavailability of extensively metabolized drugs administered rectally may be enhanced in newborns and very young infants due, in part, to their immature hepatic metabolism (Johnson, 2011). The formulation administered rectally (e.g., suppository, liquid) is another determinant in the rate and extent of absorption. For example, when diazepam was administered rectally as a solution to infants aged one to two years presenting with febrile convulsions, therapeutic drug concentrations were reached within a few minutes. In contrast, absorption of the drug from suppositories was delayed, erratic, and incomplete (Knudsen, 1977). Retention time within the rectum also affects absorption. Children aged between one to four years have a greater number of high-amplitude pulsatile rectal contractions compared to older children, which can enhance the expulsion of solid forms of drugs (suppositories) and decrease their absorption (Di Lorenzo *et al.*, 1995).

Percutaneous Absorption (i.e., through skin)

Percutaneous administration is commonly used in children for cutaneous (skin) indications. Absorption through the skin is enhanced with a higher ratio of surface area to body weight, as is the case in newborns, infants, and toddlers. This leads to higher systemic blood concentrations and possible toxicity. Skin hydration and thickness also affect absorption; relative to adults absorption is increased in pre-term newborns due to their thinner skin, and in newborns (pre-term and term) and infants due to their more hydrated epidermis (Kearns *et al.*, 2003).

Intramuscular Absorption

To avoid unnecessary pain and potential tissue damage, intramuscular administration is not common practice in pediatrics. When it must be used, water-soluble drugs are preferred to prevent the drugs from precipitating at the injection site (Berlin, 2013). Muscular contractions (which are responsible for drug dispersion) are inefficient in newborns, reducing blood flow to the skeletal muscle. Decreased muscle mass also decreases the rate of intramuscular absorption (Kearns *et al.*, 2003). In addition, sick, immobile newborns in neonatal intensive care units may lack muscle movement (Tayman *et al.*, 2011), and this may interfere with drug bioavailability. However, these factors may be offset by the presence of a higher density of muscle capillaries in this age group, resulting in efficient absorption.

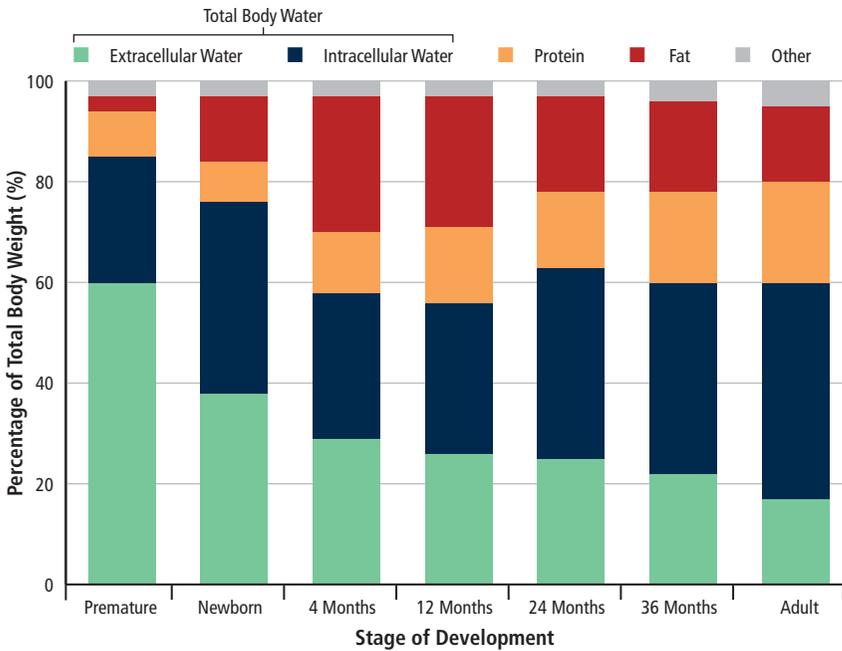
Intrapulmonary Absorption (i.e., inhaled through lungs)

Intrapulmonary administration is commonly used for infants and small children, particularly for the treatment of asthma (Fink, 2012). Aerosol particles are less efficiently delivered to infants aged less than six months due to less air movement in and out of the lungs, an inability to take a deep breath, and a short respiratory cycle. Particles therefore have a shorter residence time in the airways and this must be considered along with body weight when prescribing an appropriate dose (Fink, 2004). The size of the particles that are inhaled during this type of administration is also relevant across younger age groups. Aerosol particles are typically designed for adults and older children and large-particle aerosols are not suitable for newborns, infants, and children who have smaller pulmonary passages (e.g., bronchioles) (Amirav & Newhouse, 2012). Systemic absorption can occur following intrapulmonary administration and can result in toxicity (e.g., inhibition of growth associated with inhaled corticosteroids) (Kearns *et al.*, 2003). See Section 4.4 for further discussion on some drug delivery devices that enable better deposition of particles in the lungs of children.

3.2.2 Distribution

After reaching the bloodstream, drugs are distributed to various body organs, tissues, and cells. Apparent volume of distribution refers to the volume that would be required to contain all of the drug in the body at the same concentration as it is in the blood. While the volume of distribution is a theoretical number only, it does illustrate where the drug is likely to be present in the body (Holford, 2009). For example, a drug with a small volume of distribution (e.g., 0.15 L/kg of body weight) is likely to be concentrated in the circulation, while a drug with a larger apparent volume of distribution (e.g., 30 L/kg) is likely to be bound to tissue or stored in fat. To avoid low drug concentration and to achieve a therapeutic effect, a drug with a large volume of distribution may necessitate a loading dose.

Drug distribution is altered during childhood, primarily by developmental changes in body composition, plasma protein binding, and membrane permeability. These can affect the concentration of a medication in the blood and at its site of action and can therefore impact the drug response (Johnson, 2011; Tayman *et al.*, 2011). Body composition changes with age. Figure 3.3 compares the body composition of pre-term newborns, term newborns, infants, toddlers, and young children with 30-year-old adults. The figure indicates a higher percentage (with regard to body weight) of extracellular and total body water content and a lower percentage of protein and fat content in newborns than in adults. Relative total body water and extracellular water both decrease rapidly during the first year of life. From age one onwards, the percentage of extracellular water continues to decrease slowly while total body water remains fairly constant (~60% of body weight) (Kauffman, 2010). For water-soluble medications, the larger relative extracellular and total body water spaces in newborns and young infants result in lower blood concentrations of medications than in older children and adults (Kearns *et al.*, 2003). Measurements that compare the concentration of medications in tissues other than blood can be used along with other parameters, such as body weight, to develop a dose regimen designed to achieve a desired target concentration. Children may also have altered tissue composition due to conditions unrelated to age, such as more fat tissue (i.e., obesity) or abnormal fluid accumulation (i.e., edema); in such instances, the dosage may require further adjustment (Holford, 2009).



Extracted from Friis-Hansen (1961) and Kauffman (2010)

Figure 3.3

Estimated Proportional Body Composition of Newborns, Infants, Toddlers, Young Children, and Adults

The proportions of water, fat, and protein relative to total body weight change with age and, along with the solubility characteristics of the drug, can affect the blood concentration of a medication (Johnson, 2011). Body composition of children of various developmental stages is different from that of a 30-year-old adult. Figure was created by extraction of data on body composition from sources cited to estimate percentages of body composition by age group. Mean data were then generated to produce the figure.

The binding of drugs to circulating plasma proteins, such as albumin and alpha-1 acid glycoprotein, also affects their distribution throughout the body. Only drugs that are not bound to proteins (free fraction) are free to cross membranes, get distributed to their site of action or to tissues, and subsequently undergo metabolism and excretion. Protein binding is reduced in newborns because of both a lower concentration of binding proteins and a reduced binding affinity for the proteins that are present (Bartelink *et al.*, 2006). In addition, molecules commonly found in the body, such as bilirubin and free fatty acids, which are at higher concentrations in newborns, may bind to plasma proteins and displace drugs from their binding sites. All of these factors can increase the free fraction of highly protein-bound drugs, putting newborns at risk of adverse effects or exaggerated

therapeutic effects (Tayman *et al.*, 2011). An increase in the unbound fraction of a drug may also affect its rate of metabolism and excretion. In fact, the relevance of plasma protein binding to actual changes in the pharmacological effects of a drug has been questioned (Holford, 2009). When the amount of unbound drug in the plasma increases, the rate of elimination also increases because this rate is directly proportional to the concentration of free drug; therefore, the clinical outcome may remain unchanged (Holford, 2009). In cases where elimination cannot keep pace, more of the drug may be distributed to other tissues (e.g., the brain), resulting in toxicity.

If the cells that constitute a tissue have more permeable membranes (i.e., if the molecules of a drug can pass through the cells more easily), this can boost the therapeutic effects of a drug but can also lead to toxicity if the enhanced permeability is in a tissue where the effects are unwanted. For example, the blood–brain barrier, which normally restricts drug distribution to the brain, is more permeable in newborns and following infection, trauma, or surgery. Newborns also have reduced levels of plasma protein binding (increasing the free unbound fraction of the drug), which tends to increase drug passage across the barrier (Johnson, 2011). In addition to diffusion processes, permeability across the blood–brain barrier is also a function of the relative expression of influx and efflux transporters (discussed in Section 3.2.5), of which little is known after the neonatal period.

Although beyond the scope of this chapter, other factors associated with development or disease, such as changes in regional blood flow, acid–base balance, and cardiac output, can affect drug distribution (Rakhmanina & van den Anker, 2006). To ensure effectiveness, dosages need to be adjusted based on developmental and pathological changes in parameters, such as the volume of distribution (Holford, 2009).

3.2.3 Metabolism

Drug clearance is the most important concept when considering a rational regimen for long-term drug administration. It is a measure of the body's efficiency in eliminating drugs and dictates the maintenance dose of a drug to be given to achieve a target blood concentration. Two types of drug elimination result in drug clearance: metabolism and excretion.

Drug metabolism is the process by which medications are transformed by systems in the body. While drug metabolism is typically associated with the liver, important metabolic activities also take place in other organs such as the intestine (discussed in Section 3.2.1) or the kidneys. The liver often converts drugs to metabolites that are more water-soluble and therefore more easily excreted. Metabolism

can convert drugs into weaker or inactive forms or, alternatively, into active or toxic forms (Johnson, 2011). Each of these metabolites can circulate to target tissues and have an effect before being further broken down and excreted. For example, the use of codeine as a pain reliever largely depends on its metabolism to morphine, the principal active metabolite responsible for its analgesic effect. This reaction is catalyzed by the cytochrome P450 enzyme CYP2D6 (Dayer *et al.*, 1988). CYP2D6 is immature in newborns and infants, with competency approaching adult levels by five years of age (Treluyer *et al.*, 1991; Hines, 2008), and is known to be highly polymorphic (Madadi & Koren, 2008). Therefore, CYP2D6 activity can vary considerably between individuals depending on their age and their genetic make-up.

There are two broad classifications for human drug metabolism: Phase I reactions (which involve structural alteration of a drug molecule) and Phase II reactions (which involve conjugation with another, often more water soluble, portion of a molecule) (Strolin Benedetti & Baltes, 2003).

Phase I Enzymes

Cytochrome P450 (CYP) enzymes are responsible for a large portion of the Phase I drug metabolism reactions (Johnson, 2011). The human genome encodes almost 60 CYP genes, which have been divided into 18 families. Enzymes in three of these families (CYP1 to CYP3) are involved in the majority of drug metabolism (Hines, 2008; Nebert *et al.*, 2013). Metabolic enzymes such as those in the P450 superfamily can be induced or inhibited by medications and, as such, drugs mainly metabolized by these enzymes are at risk for drug interactions (Krau, 2013). Developmental changes significantly affect the expression patterns of these enzymes. At birth, total hepatic cytochrome P450 concentration is approximately 30% that of adult values. The expression and activity of most enzymes are low-to-absent in the fetus and their development is triggered at time of birth. Three major groups of cytochrome P450 enzymes have been described based on changes in their metabolic activities after birth (Cresteil, 1998). The first group is characterized by relatively high expression during fetal life, with rapid decline in expression after birth, and low or undetectable expression in most adults. Enzymes in the second group are expressed at relatively constant levels in the fetus, after birth, and into adulthood. The third group includes enzymes that are low-to-absent in the fetus and become active late in pregnancy, after birth, or within one to two years. The rate of maturation of the different CYP enzymes is isoform-specific; full adult activity is achieved during the first year of life for some enzymes (e.g., CYP3A4) while others reach adult levels later (e.g., late childhood for CYP1A2) (Hines, 2008, 2013). The changes in drug-metabolizing enzyme expression around the time of birth may account for the toxicity of some drugs in

newborns (Kearns *et al.*, 2003; Rakhmanina & van den Anker, 2006). Furthermore, some drugs taken by the mother during pregnancy have the potential to induce these enzymes and alter drug metabolism in newborns (Koren, 2009). The impact of metabolic immaturity of CYP450 enzymes on drug response early in life is highlighted in Box 3.1, which describes how midazolam metabolism and elimination differ between newborns and adults. Altered enzyme activity has a strong effect on the metabolism of many medications administered to children and therefore affects drug dosing regimens in this population. Failure to acknowledge these age-related differences in metabolism may translate into unwanted clinical effects.

Box 3.1

How Reduced Metabolism in Newborns Can Alter Response to Midazolam

Midazolam, a short-acting benzodiazepine, is commonly used to sedate those children in the neonatal and pediatric intensive care units who require prolonged mechanical ventilation or need to undergo invasive procedures. Midazolam is extensively metabolized by the cytochrome P450 3A subfamily to a major hydroxylated metabolite (1-OH-midazolam), which is active and excreted renally. In pre-term newborns, midazolam clearance is markedly lower compared to clearance in older children and adults (nearly 10 times lower following oral administration and 1.5 to 5 times lower following intravenous administration) with a significantly longer elimination half-life (six to eight hours in pre-term compared to one to three hours in adults). This is due to the developmental immaturity of hepatic CYP3A4 metabolism (i.e., low CYP3A4 activity) (De Wildt *et al.*, 2001, 2002). As such, pre-term newborns require much lower doses of midazolam and longer dosing intervals (for oral administration).

Failure to take into account the impact of development on midazolam clearance is associated with numerous significant potential adverse effects, such as respiratory depression, hemodynamic instability, and excessive and prolonged sedation with longer duration of mechanical ventilation and length of stay in intensive care units. Recently, “an *in vivo* maturation function for midazolam clearance from premature neonates to adults [was] developed [and] can be used to derive evidence-based doses for children” across all age groups (Ince *et al.*, 2013).

Numerous *in vivo* studies have shown that drugs metabolized by the liver exhibit an age-dependent increase in clearance (normalized for body weight) in children between 1 to 2 and 10 years of age. As a consequence, toddlers and children require a relatively higher weight-based dose to avoid therapeutic failure. The exact mechanisms underlying this observation are not fully understood. A small *in vitro* study could not demonstrate developmental differences in the amount of catalytically active drug-metabolizing enzyme per hepatocyte (Blanco *et al.*, 2000).

Another explanation for this higher weight-normalized clearance in children compared with adults is their increased liver size relative to body size. Liver mass, as a percentage of body weight, is maximal between one to two years of age and declines to adult values during adolescence (Johnson *et al.*, 2005; Seyberth & Kauffman, 2011). In support of this idea, a study evaluating the pharmacokinetics of warfarin enantiomers in pre-pubertal, pubertal, and adult Japanese patients has shown that liver mass affects hepatic metabolic capacity. Clearance of unbound oral S-warfarin was significantly greater among pre-pubertal children than among pubertal children or adults after adjusting for total body weight or body-surface area but not after adjusting for estimated liver weight (Takahashi *et al.*, 2000). However, this was not replicated in a study evaluating the clearance of antipyrine where its clearance correlated significantly with age, even after correction for liver weight (Murry *et al.*, 1995).

Phase II Enzymes

Although the developmental expression of Phase II enzymes is less established than that of Phase I enzymes, failure to recognize the impact of developmental changes on conjugation reactions may have serious consequences (e.g., *gray-baby* syndrome, associated with the administration of chloramphenicol to newborns).

For example, for the glucuronosyltransferases (UGTs), differences between isoforms result in no clear pattern for the development of UGT activity in childhood. The activity of each individual isoform must be tested with a highly selective *probe substrate* (i.e., a compound that is metabolized specifically by that isoform). The overlapping specificities of different isoforms and the lack of specific probe substrates have hampered the ability to characterize the activity of UGTs throughout development. However, there is considerable evidence related to developmental changes of one specific UGT isoform and morphine. Morphine glucuronidation mediated by UGT2B7 is present in premature infants as young as 24 weeks of gestational age. The clearance of morphine is five times lower in newborns compared with children aged 1 to 16 years; adult levels are reached somewhere between 2 to 30 months of age depending on the model used (per kg size model or allometric $\text{kg}^{0.75}$ power model), with no apparent change during adolescence (De Wildt *et al.*, 1999).

The development of other Phase II enzymes is also isoform-specific. Although some are highly active at birth (e.g., sulfotransferases), others require at least one year of life to reflect adult levels (e.g., N-acetyltransferases) (Tayman *et al.*, 2011).

3.2.4 Excretion

The second type of drug elimination is excretion. Excretion is the elimination of a medication or its metabolite(s) (active or inactive) from the body, primarily by the kidneys and to a lesser extent by the biliary system (Johnson, 2011). Medications may be eliminated unchanged from the plasma or following metabolism in the liver. Some medications are cycled through the liver and intestines to be re-absorbed in the blood and subsequently returned to the liver (enterohepatic circulation) (Tetelbaum *et al.*, 2005). If this cycling pathway is incomplete, the compound is excreted in the stool (Johnson, 2011).

Most of the developmental variations in medication excretion are due to the level of renal (kidney) maturation. At birth, kidneys are anatomically and functionally immature, and the rate at which they can filter fluid (known as the glomerular filtration rate) is much lower than it is in adults. The glomerular filtration rate increases rapidly during the first two weeks of life, as a result of an increase in renal blood flow, and approaches adult values within one year of age (Tayman *et al.*, 2011). As well, tubular secretion, an active transport process occurring in the kidneys, is immature at birth and reaches adult capacity within the first year of life. The immaturity of these processes can dramatically alter the clearance of drugs and thus necessitate age-appropriate dose regimens (Rakhmanina & van den Anker, 2006). As an example, the clearance of digoxin, which is eliminated by glomerular filtration as well as active tubular secretion, is lower in newborns compared to infants and toddlers, and failure to adjust doses accordingly will result in significant toxicity (Halkin *et al.*, 1978).

3.2.5 Drug Transporters

Drug responses result from the complex interplay of multiple processes that govern pharmacokinetics and pharmacodynamics. Over the past several decades, it has become increasingly apparent that carrier-mediated processes, or transporters, play critical roles in the overall pharmacokinetics of numerous drugs. Transporters are proteins expressed on cell surfaces of virtually all organs and tissues in the body, including intestinal epithelial cells, hepatocytes (liver), renal tubular cells (kidney), and the blood–brain barrier (Neville *et al.*, 2011; Thompson, 2011). Transporters can limit or facilitate a drug's absorption, affect its distribution to target organs, and enable its uptake and removal from hepatocytes and renal tubular cells (thereby affecting renal and biliary excretion) (Thompson, 2011). Thus, transporters can have a significant effect

on the therapeutic course of action. Transporter action can differ with age and development, and can also vary on an individual level as a result of genetic differences (Neville *et al.*, 2011).

Relatively little is known about how development affects the expression of different transporters, but this has been an area of intense study (Thompson, 2011). In drug development, research focuses on how drugs interact with efflux and influx transporters. Efflux transporters are those that transfer drug molecules out of the cell, whereas influx transporters transfer molecules into the cell. Two major groups of efflux drug transporters that have been shown to affect pharmacokinetics in children are ATP-binding cassette (ABC) protein transporters and solute carrier (SLC) transporters.

The ABC transporters are largely responsible for transporting toxic substances and drugs outside of the cellular membranes; these efflux transporters are located on intestinal epithelial cells, liver epithelial cells, the blood–brain barrier, renal tubular epithelial cells, and the placenta (Thompson, 2011). They include the ABC transporter P-glycoprotein (P-gp; also known as MDR1 or ABCB1), the breast cancer resistance protein, and multidrug resistance-associated proteins.

P-gp decreases the bioavailability of orally administered drugs by limiting their intestinal absorption. It can also limit the entry of various drugs into the central nervous system (CNS) (Giacomini *et al.*, 2010). Limited data are available on the impact of development of P-gp expression in children. In a 2013 report, intestinal P-gp expression (as measured by messenger RNA) was found to be highly variable in children aged 2 months to 18 years, without any clear maturation trajectory (Mizuno *et al.*, 2014). A separate study examining P-gp messenger RNA in fetal, newborn, and adult samples found a relatively low expression in the small intestine throughout life except in young adults (15 to 38 years old) (Miki *et al.*, 2005). A more recent preliminary report showed no significant difference in intestinal P-gp mRNA expression between newborns and adults (see Mooij *et al.*, 2013 in Mizuno *et al.*, 2014). In another recent preliminary report, hepatic P-gp expression (as measured by messenger RNA) in fetuses, newborns, infants, and children was 25 to 60 times lower than adult values (Mooij *et al.*, 2013).

In the human brain, P-gp is present in newborns (and as early as 22 weeks of gestation) although at lower levels than in adult brains (Daood *et al.*, 2008). In children, variability in the CNS expression of P-gp could lead to increased drug toxicity from CNS drugs. Varying expression can also lead to variable treatment response to chemotherapy (Neville *et al.*, 2011). For example, in some studies increased P-gp activity in leukemia cells is associated with a poor outcome in patients with acute leukemia (Steinbach & Legrand, 2007). Adults generally have a worse prognosis than children, which could be explained by the observation that P-gp activity is usually higher in acute lymphoblastic leukemia cells from adults compared to those from children (Plasschaert *et al.*, 2003).

The SLC transporters are an example of drug transporters that “are largely responsible for uptake across many cell membrane barriers, including intestinal epithelial cells, hepatocytes, and kidney proximal tubule cells” (Thompson, 2011). This group of transporters includes the organic cation and anion transporters. Variation between individuals in these transporters has been shown to cause differences in the ability to metabolize certain categories of medications (Neville *et al.*, 2011). In addition, combined data indicate that this group of transporters matures gradually, and that organic cation transporters become functional more slowly than organic anion transporters (Neville *et al.*, 2011). Intestinal peptide transporters can also bind with milk. Milk peptides are probably continuously distributed along the intestinal lining in infants receiving a milk-based diet; these peptides may compete with drugs for binding to intestinal peptide transporters (Funk *et al.*, 2012). Recent data suggest that variation in the genes coding for SLC transporters may be associated with cardiotoxicity following treatment of children with a particular class of drugs used for chemotherapy (Visscher *et al.*, 2012).

A number of drug transporters can cause drug disposition differences in children compared to adults. These differences can reach the point where an effective drug for one population is ineffective for another, and this has serious implications for drug development and utilization. Although this field is largely underdeveloped, further study into the effect of human development on drug transporters holds promise for improving future research and quality of care for children.

Table 3.1
Summary of Developmental Changes in Pharmacokinetic Processes and Their Implications

Physiological Parameter	Pre-Term Newborns	Newborns (0–27 days)	Infants and Toddlers (28 days–23 months)	Children (2–11 years)	Adolescents (12–17 years)	Pharmacokinetic Implications
Enteral Absorption — Gastric pH	Similar to newborn.	Neutral at birth (pH 6–8), falls to a pH of 1–3 by 24 hours; returns to neutrality by day 8, then slowly begins declining.	Slowly declines starting ~ one week after birth. Similar to adult (pH 2–3) by age 2.	Similar to adult.	Similar to adult.	Acid-labile drugs are absorbed more efficiently early in life. Ionized drugs are poorly lipid-soluble, so they cannot cross biological membranes easily; thus, drugs that are weak organic acids, which remain un-ionized in highly acidic environments, are more easily absorbed at a low pH. Basic drugs are absorbed more rapidly at higher pH.
Enteral Absorption — Gastric Emptying (rate of removal from stomach)	Irregular and delayed compared to adults. Can be variable (dependent on composition of meal).	Irregular and delayed compared to adults. Can be variable (dependent on composition of meal).	Delayed and variable in young infants; approaches adult values by 6–8 months and then increases beyond adults.	Slightly increased compared to adult.	Similar to adult.	Delayed gastric emptying results in delayed drug absorption. Time to peak concentration may be delayed and peak concentration may be lower (but the area under the curve usually not affected).
Enteral Absorption — Intestinal Transit Time	Unknown.	Can be longer (i.e., slower) than adults due to decreased intestinal motility but variable, depending on feeding or dysfunction such as diarrhea, which shortens transit time.	Shorter (i.e., faster) than adults due to increased intestinal motility.	Slightly increased compared to adult.	Similar to adult.	When transit time is longer, poorly water-soluble drugs may be better absorbed. When intestinal transit time is shorter, sustained release products are not readily absorbed.

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Physiological Parameter	Pre-Term Newborns	Newborns (0–27 days)	Infants and Toddlers (28 days–23 months)	Children (2–11 years)	Adolescents (12–17 years)	Pharmacokinetic Implications
Enteral Absorption — CYP3A4 Intestinal Metabolism	Unknown.	Decreased activity compared to children older than 12 years.	No statistically significant difference in intestinal CYP3A4 activity from 3 months until adolescence.			Lower intestinal CYP3A4 activity decreases the first pass intestinal effect with an increase in drug bioavailability.
Enteral Absorption — P-gp-Mediated Intestinal Transport*	Unknown.	Limited data with conflicting results.	Limited data suggesting adult pattern is reached by 2 months of age.			No consistent developmental effects; high levels of P-gp can limit entry of drugs into intestinal cells, thereby decreasing bioavailability.
Rectal Absorption	Unknown.	Can be increased as a result of reduced first pass effect (in part, due to immaturity of hepatic drug-metabolizing enzymes). Can be affected by formulation (liquid or suppository).	Can be increased as a result of reduced first pass effect (in part, due to immaturity of hepatic drug-metabolizing enzymes). Can be affected by formulation (liquid or suppository).	Near-adult pattern.	Similar to adult.	When properly formulated drug products are administered, rectal administration may be very efficient in newborns and young infants.
Percutaneous Absorption	Similar to newborn, except in addition, outermost layer of epidermis is thinner.	Ratio of surface area to body weight is higher. Skin is more hydrated.	Similar to newborn.	Near-adult pattern.	Similar to adult.	For newborns (especially pre-term newborns) and infants, more efficient absorption of drugs applied topically and thus potential for toxicity. Amount of a drug applied to the skin should be reduced.

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Physiological Parameter	Pre-Term Newborns	Newborns (0–27 days)	Infants and Toddlers (28 days–23 months)	Children (2–11 years)	Adolescents (12–17 years)	Pharmacokinetic Implications
Intramuscular Absorption	Similar to newborn, except sick, immobile pre-term newborns may have less efficient absorption than term newborns due to reduced muscular contractions.	Inefficient muscle contractions and reduced blood flow to muscles reduce absorption, but these factors may be offset by a higher density of muscle capillaries.	Younger infants are similar to newborns.	Similar to adult.	Similar to adult.	Lack of drug dispersion may reduce absorption in newborns, while higher density of muscle capillaries may result in efficient absorption.
Intrapulmonary Absorption	Pre-term newborns have a high respiratory rate, which reduces the length of time that particles reside in the lower respiratory tract and reduces efficiency of aerosol delivery.	Less efficient delivery of aerosol compared to children older than 6 months and adults. Less large-particle aerosol is deposited in the lungs than in children older than 4 years and adults.	Similar to newborns. Behavioural factors are important (e.g., crying reduces aerosol deposition). Alveoli continue to develop until ~2 years of age.	Reduced large-particle aerosol deposition in the lungs until ~4 years of age due to particles becoming trapped in the small airways.	Similar to adult.	Better therapeutic outcomes in children might be achieved using aerosols with smaller particles. Dose must be adjusted carefully to account for lower deposition efficiency in children.
Distribution — Body Composition	Relative total body water can be very high. May also be increased due to conditions such as patent ductus arteriosus, which cause fluid overload. Fat content can be as low as 1% of body weight in extreme pre-term newborns.	High relative total body water (~80% of body weight) and extracellular water (~40%). Low fat content (~15%).	Relative total body water still high, but decreases (~60% of body weight by 6–12 months), with a decrease in extracellular water (~30% by 6–12 months). Increase in fat content (~25% at 4 months).	Relative total body water similar to adult (~60% of body weight). Relative extracellular water gradually decreases with age during childhood.	Similar to adult.	In newborns and young infants, higher body water as a proportion of total body weight results in a larger apparent volume of distribution and therefore lower blood concentration of drugs that distribute to water spaces. For drugs that bind to muscle or fat, the apparent volume of distribution is reduced.

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Physiological Parameter	Pre-Term Newborns	Newborns (0–27 days)	Infants and Toddlers (28 days–23 months)	Children (2–11 years)	Adolescents (12–17 years)	Pharmacokinetic Implications
Distribution — Plasma Proteins	Unknown.	Concentration of binding proteins in plasma is lower than adult. Plasma proteins have lower binding capacities.	Younger infants are similar to newborns and adult plasma protein concentrations are reached by age 1.	Similar to adult.	Similar to adult.	In newborns, for highly protein-bound drugs, the level of free, unbound drug is higher, which increases the potential for toxicity.
Distribution — Membrane Permeability	Blood–brain barrier is underdeveloped (more permeable).	Blood–brain barrier still not mature at birth but permeability begins decreasing after birth.	Unknown.	Unknown.	Unknown.	In newborns (especially pre-term newborns), drugs may gain access to the central nervous system and toxicity may result.
Metabolism — CYP450 Enzymes	Metabolic activity reduced compared to term newborns.	Activity of most CYP450 enzymes is much lower than in adults. Expression of others (such as CYP3A7) disappears after birth.	Activity of some CYP450 enzymes matures during the first year of life to reach adult values (CYP2C9, CYP2C19, CYP3A4).	Activity of some CYP450 enzymes still reduced and may not reach adult levels until age 5 (CYP2D6) or late childhood. In older infants and children, higher hepatic clearance than adult when normalized for body weight.	Similar to adult.	In newborns and young infants, need to decrease dose and increase dosing interval to avoid toxicity. In older infants and children, need to administer higher weight-based dose to avoid inefficacy.

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Physiological Parameter	Pre-Term Newborns	Newborns (0–27 days)	Infants and Toddlers (28 days–23 months)	Children (2–11 years)	Adolescents (12–17 years)	Pharmacokinetic Implications
Metabolism — Phase II Enzymes	Unknown.	Deficient glucuronidation and acetylation; efficient sulphate conjugation.	Isoform-specific developmental profile. Expression highly variable for all Phase II enzymes.			In newborns, need to decrease dose and increase dosing interval for drugs metabolized by glucuronidation or acetylation.
Elimination — Kidney Function	Lower glomerular filtration rate than term newborns; level of function increases with gestational age and body weight (i.e., lower function in more severely premature newborns).	Kidneys are anatomically and functionally immature, with lower levels of glomerular filtration and tubular secretion.	Glomerular filtration and tubular secretion mature by ~12 months.	Similar to adult.	Similar to adult.	In newborns and young infants; accumulation of renally excreted drugs and increased elimination half-life. Need to adjust the dose to avoid toxicity.

Data Source: Treluyer *et al.* (1991); Van den Anker (1996); Kearns (2000); Johnson *et al.* (2001); Alcorn and McNamara (2002); Kearns *et al.* (2003); Strolin Benedetti and Baites (2003); Fink (2004); Miki *et al.* (2005); Bartelink *et al.* (2006); Rakhmanina and van den Anker (2006); WHO (2007); Hines (2008); Johnson and Thomson (2008); Van den Anker (2010); Johnson (2011); Tayman *et al.* (2011); Amirav and Newhouse (2012); Berlin (2013); Mizuno *et al.* (2014)

* Data derived for intestinal P-gp (ABCB1) mRNA expression.

3.3 PHARMACODYNAMICS AND HUMAN DEVELOPMENT

Pharmacodynamics is the general term used to denote the biochemical and physiological effects of a drug and its mechanism(s) of action. It refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects (Johnson, 2011). As highlighted in Figure 3.1, human development as well as factors such as genetic variation, disease state, and nutritional status can affect pharmacodynamics (and pharmacokinetics) and the overall clinical response to a drug. Pharmacodynamics involves many complex variables, including drug targets (receptors, ion channels, enzymes, and carrier proteins), signalling mechanisms, effectors, and chemical interactions (Tayman *et al.*, 2011). The number of receptors present (explained in detail below), their localization in different tissues, and their likelihood of binding to medications are all factors that can change throughout human development. As such, demonstration of efficacy in adults does not guarantee similar beneficial effects and safety profiles in children, and pediatric trials are needed to evaluate drug efficacy and toxicity in children.

Together with pharmacokinetic information, pharmacodynamics helps to explain the relationship between a medication dose and the observed response, and is central in determining optimal dosing regimens (Tayman *et al.*, 2011). For example, studies have shown that, compared to adults, prepubescent children experience an augmented response to warfarin (an anticoagulant drug used widely in children). This greater sensitivity to warfarin appears to be independent of pharmacokinetic differences (i.e., even if dosages are adjusted to generate similar blood concentrations of unbound warfarin in children and adults, children may still experience a greater anti-coagulant effect), and the exact mechanism remains unknown. Therefore, both pharmacokinetics and pharmacodynamics must be taken into account to avoid therapeutic failure (i.e., development or progression of clots) or adverse effects (i.e., increased risk of bleeding) (Takahashi *et al.*, 2000). Another example is the impact of development on the immunosuppressive effects of cyclosporine. Infants have been shown to have a greater immunosuppression response to cyclosporine than older children and adults. This is likely related to immaturity of the T-lymphocyte response in the infant and has important therapeutic implications for dosing (Marshall & Kearns, 1999). Although data on the impact of development on pharmacodynamics are currently scarce, some evidence on how human development can specifically affect drug receptors is available. The following discussion is only a brief introduction to the current state of knowledge because there is little available evidence and research is lacking in this important area.

3.3.1 Drug Receptors

Drug receptors are generally defined as biological components on a cell surface that selectively bind to molecular drug signals and initiate pharmacological responses (Lambert, 2004; Tayman *et al.*, 2011). Four main categories of receptors exist: ligand-gated ion channels, G-protein-coupled receptors, enzyme-linked receptors (e.g., tyrosine kinase-coupled receptors), and nuclear receptors (e.g., steroid receptors) (Lambert, 2004). Each of these corresponds to different types of drugs and molecules. For example, tyrosine kinase-coupled receptors respond to biologics such as insulin and growth hormones, and G-protein-coupled receptors respond to opioids such as morphine (Lambert, 2004). Data from animal models have shown the effect of development on the expression of opioid receptors, namely that certain types of receptors are more prevalent just after birth, with other types emerging later in childhood (Neville *et al.*, 2011). Table 3.2 provides some information on the development of different drug targets either in animals or humans, highlighting the potential consequences of these developmental variations on the drug response in children.

Information is lacking on the effect of human development on variations in receptor number and affinity, and on the impact of these variations on drug response. There is some indication that receptor variation may contribute to pharmacological responses at various ages. For example, wheezing toddlers respond poorly to a class of drugs for asthma — beta₂-adrenergic agonists — and this may be partly explained by a reduced number of beta₂-adrenergic binding sites (Seyberth & Kauffman, 2011). A second example is that of major depressive disorder, which is diagnosed at a rate of 2.5% to 4% in children (Bylund & Reed, 2007; Murrin *et al.*, 2007). While a variety of antidepressant drugs can provide effective treatment in adults, only some antidepressant drugs within the selective serotonin reuptake inhibitor (SSRI) class have been demonstrated to be clinically effective in children and adolescents. Other classes of antidepressant drugs, such as tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), have not been shown to be clinically effective in children in recent studies (Murrin *et al.*, 2007). This difference is due to the fact that the system affected by tricyclic antidepressants and MAOIs (the noradrenergic system) matures more slowly than the serotonergic system, which is the target of SSRIs. Animal and human studies indicate that serotonin receptor binding, serotonin synthesis capacity, and serotonin uptake sites are generally higher in the developing brain than in the adult brain, declining toward adult values by puberty (Chugani *et al.*, 1999; Murrin *et al.*, 2007). Even in situations where clinical efficacy may have been proven, for the majority of antidepressant drugs, the beneficial effects may not outweigh the risks in children (Bylund & Reed, 2007; Mulla, 2010).

Table 3.2

Developmental Changes in Drug Targets and Their Potential Consequences for Children

Examples of Relevant Drug Targets	Class of Drug	Developmental Profile	Source of Developmental Data	Potential Consequences in Children
Ligand-Gated Ion Channel	Antiepileptics targeting the GABA [*] ergic system.	GABA switches from an excitatory to an inhibitory neurotransmitter shortly after birth and GABA _A receptors change in density and distribution during development.	Animals and humans.	Paradoxical seizures.
Carrier Protein	Antidepressants inhibiting neuronal transport (reuptake) of norepinephrine.	Neurodevelopmental delay in norepinephrine system.	Animals.	Lack of effect of tricyclic antidepressants.
G-Protein Coupled Receptor	Opioid analgesics.	Changes in opioid receptor expression.	Animals.	Increased sensitivity to opioid analgesics.
Ion Channels	Cardiovascular drugs prolonging QT interval (e.g., sotalol, amiodarone).	Maturation of myocardial potassium channels.	Animals.	Increased propensity for QT interval prolongation, which may induce cardiac arrhythmia.

Data Source: Lambert (2004); Mulla (2010)

* GABA refers to gamma-aminobutyric acid

3.4 PHARMACOGENOMICS AND PHARMACOGENETICS IN THE DEVELOPING CHILD

Pharmacogenomics is the integration of pharmacology and genomics, applying genome-wide technologies and strategies to identify new targets for disease diagnosis or progression, drug development, factors predictive of therapeutic efficacy, and risk of adverse drug reactions (ADRs). *Pharmacogenetics* is the study of individual genetic variations that give rise to variable drug responses among individuals (Neville *et al.*, 2011). These fields of study have become increasingly important for the development and prescription of effective medications and for advancing understanding of variability in pharmacokinetic and pharmacodynamic processes and overall drug response (Piana *et al.*, 2012). For

example, a standard dose of the same medication may have poorer effectiveness in 20% to 30% of patients, and may cause safety issues in 5% to 15%. Before the advent of pharmacogenomics, these findings were known to be a result of differences in metabolic clearance or disease factors between individuals, but the sources of these differences had not been identified (Piana *et al.*, 2012). Pharmacogenomics (including pharmacogenetics) now provide evidence that genetic variation is responsible for at least part of this inter-individual variability; therefore, researchers must take into account not only ADME changes and pharmacodynamic differences throughout development but also variations in individual and population genetics.

For example, research has shown some important genetically determined variations in drug response among ethnic groups, as is the case with cytochrome CYP2D6. A polymorphism of CYP2D6 that increases the risk of serious adverse events from codeine is much more common among children of Mediterranean and African ancestry than among children of Northern European ancestry (Madadi *et al.*, 2007). Another example involves genetic variations in the beta2-adrenergic receptor among individuals that can result in a decreased response to salbutamol (albuterol) following repeated use (Neville *et al.*, 2011). In treating children with asthma, awareness of their genetic characteristics as well as their stage of development can contribute to the prescription of effective medications and doses (Finkelstein *et al.*, 2009). This knowledge is also useful for the future development of alternative drugs. Other examples of important Canadian research exploring the interrelationships between human development, pharmacokinetics, pharmacodynamics, and genetic variation include:

- genetically determined variations in drug transporter activity and anthracycline toxicity in children with cancer in London, Ontario and Vancouver, British Columbia (Visscher *et al.*, 2012);
- mechanisms of genetically determined cisplatin-induced ototoxicity in children in Vancouver, British Columbia (Ross *et al.*, 2009; Pussegoda *et al.*, 2013); and
- genetic determinants of responsiveness to corticosteroids in childhood asthma in Montréal, Quebec (Ducharme, 2013).

Pharmacogenomic data have the potential to influence the quality of care for children by contributing knowledge that can be used to develop individualized pharmacotherapies that maximize efficacy and minimize toxicity (Ma *et al.*, 2012). Genetic variation can affect enzymes, transporters, and receptors that can impact the pharmacological response to medications. Examples include risk to children who are either CYP2D6-poor or ultra-rapid metabolizers when taking medications metabolized by that cytochrome. For example, in the case of codeine, a child who is a poor metabolizer is unable to transform codeine into morphine and thus the desired therapeutic result of pain alleviation

cannot take place; an ultra-rapid metabolizer transforms too much codeine into morphine, leading to risk of adverse effects (e.g., respiratory depression) (Wong *et al.*, 2012). There is also the example of the risk of potentially lethal Stevens–Johnson syndrome in children with the HLA-B*15:02 allele treated for epilepsy with carbamazepine (Mrazek & Lerman, 2011).

Pharmacogenomic information is most relevant to clinical practice when a genetic variation in response to a given drug has significant pharmacological implications, when the genetic variation in the population is common, or when genetic data are easier to obtain (Ma *et al.*, 2012).

Genetic testing could prove useful in designing effective therapeutic regimens in children with a number of conditions in which there is known genetic variation and high clinical relevance. In addition, technology for obtaining and analyzing genetic information is constantly evolving, presenting new opportunities for research and care. For example, new methods of analyzing genetic information can identify disease-causing genes more quickly, at lower cost, and from a smaller number of patients (Majewski *et al.*, 2011; Boycott *et al.*, 2013). Using these approaches, research is uncovering more about the genetic etiology of diseases, and can lead to improved accuracy in diagnoses and treatment.

The relationship between genotype and phenotype (the observable physical or biochemical characteristics of an organism, as determined by both genetic make-up and environmental influences) is not always straightforward. While an individual's genotype remains the same throughout his or her lifetime, the expression of genes can change throughout growth and development, causing individuals to exhibit different phenotypes. The extent to which an individual's genotype matches his or her phenotype is termed *genotype–phenotype concordance*. This is especially an issue for newborns, as *discordance* between genotype and phenotype is often seen at birth. For example, genetic testing may indicate that a newborn has a genotype associated with certain pharmacokinetics, but in fact the newborn's pharmacokinetics do not match those of her genotype, leading to incorrect conclusions about dosage adjustments. Without knowing genotype–phenotype concordance, informed treatment based on pharmacogenetic data assumes that “(i) the nature of the genotype–phenotype relationship has been established in an adult population and (ii) the drug-metabolizing enzyme or transporter activity in pediatric patients at the extremes of the phenotype distribution (i.e., poor metabolizers and ultrarapid metabolizers) has matured to the extent that they can be classified from genotype data as reliably as can adults” (Leeder & Kearns, 2012). This can be further complicated by the

presence of additional factors that can influence this genotype–phenotype relationship, such as drug–drug interactions or disease states (e.g., infection, inflammation). Ultimately, while gene-directed drug therapy and diagnosis hold considerable promise, limitations remain on the ability of these approaches to define optimal drug therapy. These limitations include the need for genotype–phenotype correlation and the problem of using genetic approaches to direct therapy (e.g., with HLA screening and testing), which may deny useful therapy to children who might otherwise have tolerated it.

3.5 APPROACHES TO INVESTIGATE PHARMACOKINETICS AND PHARMACODYNAMICS IN CHILDREN

3.5.1 Modelling and Simulation

Modelling is defined as using mathematical language to describe and quantify biological systems and their interactions with chemical and biological entities (i.e., drugs and biologics). *Simulation* refers to the use of these models to make quantitative predictions of the behaviour and the dynamics of biological systems (Manolis & Pons, 2009; Bellanti & Della Pasqua, 2011). The use of these approaches has gained popularity in pediatric drug development and pharmacotherapy as major advances in computational technologies have yielded novel possibilities for data analysis and can potentially decrease the number of children to be included in trials.

Types of Models

Modelling and simulation (M&S) techniques enable the optimal use of developmental pharmacokinetic data to predict dose–exposure relationships in different age groups (e.g., population pharmacokinetic and physiologically based pharmacokinetic models). Because data on the effects of age on pharmacodynamics are limited (see Section 3.3) and because outcome measures are not always standardized or applicable for children (see Section 5.7.3), pharmacodynamic models to predict exposure–response relationships in children are less common (Manolis *et al.*, 2011; Barrett *et al.*, 2012). Instead of predicting the dose to administer to children by scaling of adult doses using parameters such as body weight, which fails to account for the developmental differences in ADME processes discussed in Section 3.2 (Johnson, 2008), these pharmacokinetic and pharmacodynamic models can ultimately lead to evidence-based dosing recommendations for children. Both proper internal and external validation of the models are important steps to test the robustness and reliability of their predictive performance before model-based dosing algorithms are used in clinical trials or in clinical practice.

Although M&S cannot replace clinical studies in children, these techniques are typically used in conjunction with clinical trials. They may be applied before trial completion to optimize trial designs (e.g., as decision tools for selecting dose ranges, sampling schemes, outcome measures) or after trial completion (e.g., as tools for analyzing pharmacokinetic and pharmacodynamic data from pediatric studies) (Bellanti & Della Pasqua, 2011; Barrett *et al.*, 2012).

To build a physiologically based pharmacokinetic (PBPK) model, relevant anatomical, physiological, biochemical, and pharmacogenetic parameters that affect ADME are used to inform mathematical equations that predict pharmacokinetics (Manolis *et al.*, 2011). The required inputs for constructing a PBPK model include information on properties of the drug, knowledge of its target organs (i.e., based on animal or adult data), the delivery route and dose that will be used, and the physiology of the pediatric subject in question (e.g., organ weight, organ-specific blood flow, developmental state of clearance mechanisms) (Barrett *et al.*, 2012). Prediction of drug exposure using PBPK models is of special interest for newborns and young infants.

Population pharmacokinetic (POP-PK) models consider the population rather than the individual, allowing for estimation of within- and between-subject variability and for identification of patient characteristics (known as covariates) that are predictors of between-subject variability (e.g., age, sex, body weight, genotype, ethnicity, liver and renal function, co-medications, disease state) (Anderson *et al.*, 2006; Vinks, 2011). POP-PK models involve three basic components: (i) a structural model to describe pharmacokinetics; (ii) a statistical model describing within- and between-subject variability; and (iii) an error model that accounts for the residual variability. Once a basic model has been identified, potential explanatory covariates for between-subject variability are tested. As growth and development are two major aspects affecting ADME processes in children and not adults, they are always investigated by using size and age as covariates (Bellanti & Della Pasqua, 2011; Vinks, 2011). POP-PK models can analyze data collected from patients across different studies to predict the behaviour of a drug. This approach offers the possibility of gaining integrated information on pharmacokinetics from sparse data (Bellanti & Della Pasqua, 2011) but also from relatively dense data or a combination of both.

In an effort to test an innovative design and predict the outcome of a trial, a simulation of the entire trial may be performed. Such simulation requires pharmacokinetic and pharmacodynamic data to construct a drug model, knowledge of the disease under study to construct a disease model, and information — such as expected adherence rate and trial drop-out rate — to construct a trial model (Bellanti & Della Pasqua, 2011).

Advantages of Modelling and Simulation for Pediatric Studies

A major advantage of M&S in pediatric drug development is that it provides an opportunity to investigate different clinical scenarios before enrolling any children in a study. Furthermore, it enables the testing of situations that are not possible to create in actual clinical trials, for example, overdosing (Bellanti & Della Pasqua, 2011). By using M&S to choose initial dose ranges and rationalize decisions about study design, researchers can avoid including unnecessary or irrelevant treatment arms, thereby minimizing the total number of children required for clinical trials. As mentioned above and in Section 3.6.1, multiple features of population modelling approaches, such as POP-PK, are ideal for children. Population modelling allows pharmacokinetics to be investigated in small populations if necessary, since it is able to utilize data that have been pooled from small cohorts of patients in different studies. This may be particularly valuable for the study of drugs in children with rare diseases where sample sizes are extremely limited (Bellanti & Della Pasqua, 2011). Even when sample sizes are larger, this approach may still be useful if there is a need to reduce the total number of samples taken from each patient (sparse sampling) (Manolis *et al.*, 2011). Furthermore, population-based methods allow flexibility in terms of sampling times, which may be scheduled around clinical procedures or outpatient appointments (Anderson *et al.*, 2006).

Current and Future Uses of Modelling and Simulation Techniques

With the introduction of new regulations, such as the EMA's *Paediatric Regulation*, sponsors, investigators, and regulatory agencies are becoming more familiar with modelling techniques and recognizing their value in assisting with the planning of pediatric drug studies (Barrett *et al.*, 2012). As a result of the *Paediatric Regulation*, Paediatric Investigation Plans (PIPs) are evaluated by the Paediatric Committee and given either a positive or negative opinion (see Section 2.3.1). A study of all positive PIP opinions from July 2007 to January 2010 revealed that 47 of 210 specifically referenced M&S (Manolis *et al.*, 2011).

The pharmaceutical industry has contributed to the advancement of model-based drug development with the creation of the Simcyp® Population-based Simulator, a commercially available software package used by many major pharmaceutical companies. The simulator started as a simple drug–drug interaction calculator. Through the input of a consortium of leading pharmaceutical companies as well as collaborations with regulatory bodies and academic centres, the calculator has evolved into software that can perform whole body PBPK modelling, pharmacodynamics modelling, and modelling of time-variant physiology in children as they develop (Jamei *et al.*, 2013). In fact, a simulator specific to children (Simcyp® Paediatric) has also been designed (Simcyp, 2014).

Currently, more publicly available data are needed to validate and improve models. In one study, the predictive validity of a PBPK model developed with Simcyp® software was tested for 11 drugs in 2000 virtual subjects aged 0 to 18 years. Using this model, 70% to 100% of predicted clearance values were within two-fold of observed values, with the lowest accuracy for newborns and the highest accuracy for infants and adolescents (Johnson *et al.*, 2006). The performance of the model was not evaluated prospectively (observed values were from published studies). Although the validity of PBPK models has been demonstrated for drugs administered intravenously, their ability to predict systemic drug exposure following oral administration is much less reliable (Barrett *et al.*, 2012). Furthermore, although PBPK and POP-PK models are better developed and understood by drug manufacturers and regulators, more information about the effect of development on pharmacodynamics is needed to refine models with a pharmacodynamic component (Manolis *et al.*, 2011).

M&S will likely continue to play an increasing role in pediatric drug development, specifically in helping researchers navigate through the FDA's pediatric study decision tree to decide which studies are necessary, how they will be designed, and whether they will be able to support the use of extrapolation (see Chapter 5 for discussion of extrapolation and the FDA's decision tree) (Bellanti & Della Pasqua, 2011; Manolis *et al.*, 2011).

3.5.2 Approaches to Facilitate Pharmacokinetic Studies in Children

Traditional techniques for collecting biological samples in adults may need to be modified to better suit the needs of children. As mentioned in Section 3.6.1, the typical procedure for a pharmacokinetic study in adults (collecting multiple blood samples of relatively high volume) may not be appropriate for small children since their total blood volume is lower than that of adults (Laughon *et al.*, 2011).

Pharmacokinetic studies can be modified in several ways to reduce pain, distress, and blood loss in children (particularly newborn infants). These methods are endorsed by major organizations such as the FDA and WHO (FDA, 1998; WHO, 2011). Examples include using alternatives to blood such as saliva, scavenged sampling (using residual blood that was drawn for medical care), sparse (infrequent) sampling, dried blood spot sampling (collecting ultra-low volumes of blood on blotting papers), microassays, and multiple-drug assays (simultaneously measuring the concentration of several drugs in one sample) (Ashman *et al.*, 2011; Laughon *et al.*, 2011). These techniques have been used successfully to analyze the concentration of several antimicrobials and antivirals in pediatric populations (see Laughon *et al.* (2011) for a review of these studies). Saliva samples can often be used as an alternative to blood or to collect DNA.

Genetic differences in drug-metabolizing enzymes can be detected by analyzing DNA samples (Dempsey *et al.*, 2013) (see Section 3.4 on pharmacogenomics and pharmacogenetics). The advantages and disadvantages of these methods are reviewed in Table 3.3.

Table 3.3
Novel Techniques for Pharmacokinetic Studies in Children

Technique	Advantages	Disadvantages
Sample Collection Techniques		
Saliva collection as an alternative to blood collection	<ul style="list-style-type: none"> • Non-invasive. • Can be used to measure the concentrations of several drugs (e.g., caffeine, anticonvulsants, codeine) and to collect DNA for genotyping. • Older children can simply be asked to spit in a cup and younger children can chew on gauze or Salivettes® (cotton pads that come packaged in plastic tubes). 	<ul style="list-style-type: none"> • For pre-term infants, commercially available products such as salivettes are difficult to use and saliva volumes are insufficient. • Correlation between blood and saliva concentrations must be carefully studied to validate this method.
Scavenged sampling (using residual blood drawn for medical care)	<ul style="list-style-type: none"> • No additional risk or discomfort for the child since the need for vascular puncture specifically for the study is avoided. • Several samples per infant likely to be available. 	<ul style="list-style-type: none"> • Accuracy in timing of sampling is not controlled by researcher so may not be useful for certain analyses. • Uncertainties around sample storage and accurate recording of collection time may make results less reliable. • Residual blood volume may be low.
Sparse sampling combined with a POP-PK approach	<ul style="list-style-type: none"> • A small number of samples (e.g., 2–4 per patient) can be collected at various routine clinical visits for patients who are already receiving the drug therapeutically. • Samples are taken from a larger population than would be typically used for a traditional pharmacokinetic study, so the stress on each patient is minimized. • If the study is designed well, analysis of data using a POP-PK model can predict the average behaviour of a drug in a given population as well as variability within and between patients. 	<ul style="list-style-type: none"> • Planning for these studies can be complex: the study population should include enough patients from all age groups for which the drug is intended and enough patients with and without other factors (e.g., pre-existing conditions) if these are to be studied in relation to the drug. • Some knowledge of the pharmacokinetics of the drug may be needed to develop an appropriate sampling scheme.

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Technique	Advantages	Disadvantages
Dried Bloodspot Collection (involves collecting a few drops of blood on blotting paper)	<ul style="list-style-type: none"> • Ultra-low sample volume is required. • Technically simple (parents or older children can collect blood themselves with finger or heel prick), which allows sampling at remote locations. • Once dry, blood spots can be stored at room temperature and shipped using regular mail. • Easy shipping allows central processing in a single lab, which reduces site-to-site variability. 	<ul style="list-style-type: none"> • Usually not possible to perform a second assay on the sample, since the entire drop of blood will need to be processed for most assays. • Technique is not yet standard practice and requires validation (e.g., by comparing results from dried bloodspot sampling and standard blood sampling in adults).
Analysis Techniques		
Microassays	<ul style="list-style-type: none"> • Allow for the analysis of drug concentrations in ultra-low sample volumes (less than 0.1 mL) using a combination of liquid or gas chromatography and mass spectrometry. • Can measure multiple drugs in the same sample during a single run (see Multiple Drug Assays below). 	<ul style="list-style-type: none"> • Mass spectrometry requires expensive equipment and dedicated, trained personnel to operate. • Other microassay techniques (e.g., drug immunoassays) are simpler and more conducive to automation in the lab, but suffer from cross-reactivity issues between compounds that are structurally similar.
Multiple Drug Assays	<ul style="list-style-type: none"> • Allow the concentration of multiple drugs to be measured in the same sample in a single run, resulting in maximal data output from minimal biological material and reduced analytical workload. • Ideal for children, who are often treated with multiple drugs simultaneously (e.g., antimicrobials). • In a clinical trial setting, can increase efficiency, since it is unnecessary to develop individual assays for each drug. 	<ul style="list-style-type: none"> • Sampling times must be chosen carefully to capture multiple drugs. • Same technical issues as Microassays above.

Data Source: FDA (1998); Garcia *et al.* (2006); Ashman *et al.* (2011); Laughon *et al.* (2011); Brandhorst *et al.* (2012)

Other techniques, which are not necessarily for pharmacokinetic analyses, exemplify the rapid advancements that are making pediatric monitoring and research less distressing for children. For example, pulse oximetry is a non-invasive method for detecting oxygen saturation levels that were previously measurable only by analyzing blood samples. Pulse oximetry is based on the principle that hemoglobin in the blood absorbs different wavelengths of light depending on its level of oxygenation. Thus, it allows oxygen saturation to be measured using a device that includes a probe to emit light and a photosensor to measure wavelengths passing through the tissue. The device is simply attached

to a finger or earlobe. Continuous pulse oximetry monitoring is a standard of care in pediatric intensive care units (Sinha *et al.*, 2013; Ross *et al.*, 2014). More recently, near-infrared spectroscopy has been developed as a non-invasive diagnostic tool to monitor regional tissue oxygenation, which reflects perfusion status. It can be used to “continuously and simultaneously monitor tissue perfusion in different organ systems at the bedside without interrupting routine care” (Marin & Moore, 2011). This technique holds promise as a non-invasive way to evaluate the efficacy or safety of different pharmacological interventions in children (Chock *et al.*, 2011).

Reluctance to perform pharmacokinetic studies in children has been fuelled — at least in part — by the perception that the technical challenges involved are insurmountable. However, although certain populations, such as critically ill infants and children, present specific technical challenges, researchers have performed pharmacokinetic studies in these populations for many years, even when the studies required multiple blood samples from each participant (for an example, see Reed *et al.* (1996)). Furthermore, innovations such as M&S and microassays have addressed some of the existing challenges, making it even more feasible to carry out these studies in children. Nonetheless, more studies are still needed, particularly in understudied vulnerable populations such as pre-term infants, children receiving extracorporeal life support, and obese children (Laughon *et al.*, 2011).

3.6 ADDRESSING KNOWLEDGE GAPS

3.6.1 Pharmacokinetics and Pharmacodynamics

One obstacle to conducting pharmacokinetic trials is the need to monitor drug concentrations through repeated blood sampling. Such sampling can be challenging in newborns, particularly those that are pre-term (Laughon *et al.*, 2011). As mentioned in the previous section, certain approaches and new technologies can be used to minimize patient stress and ensure proper data are obtained. These data can then be analyzed using methods that include information from a range of individuals to predict behaviour of a drug, for example, POP-PK and PBPK models (Bellanti & Della Pasqua, 2011). Furthermore, newer study designs where pharmacokinetic data are obtained as a part of the regular standard of care have been put forward and appear as interesting alternatives in some situations. For example, the Pediatric Trials Network in the United States began the PTN POPS study (the full study name is pharmacokinetics of understudied drugs administered to children per standard of care) in 2011 (PTN, 2013). The study enrolls children of various ages who are already receiving drugs prescribed by their physicians. When blood is needed for other laboratory tests, an additional sample is taken for pharmacokinetic studies. The goal of

this study is to develop pediatric-specific dosing guidelines by characterizing the pharmacokinetics of drugs in children using an approach that minimizes invasiveness, inconvenience, and stress for participants.

In spite of these developments, there remains a general lack of data on the impact of pediatric developmental processes involved in pharmacokinetics. This gap is most striking for pre-term and term newborns as well as infants, the groups undergoing the most significant developmental changes in drug disposition (occurring during the first year of life). One of the challenges in administering medications to newborns involves accounting for the rapid changes in drug clearance that can occur during the first week of life, often due to changes in drug-metabolizing enzymes. One day post-birth, clearance rates of some medications can be much lower in newborns than adults, but rates may increase several-fold as early as one week after birth, thereby necessitating higher doses to maintain efficacy (Mukherjee *et al.*, 2009). Although gaps also exist for adolescents, pharmacokinetic knowledge gleaned from adults is usually more easily transferable to this older age group. However, data exist to support the hypothesis that sex and growth hormones alter drug-metabolizing enzymes during puberty. A research agenda for expanding these data was developed at a key workshop in 1994, but information is still limited (Kennedy, 2008).

The development of drug transporter expression — now increasingly recognized as a crucial determinant of safety and efficacy for many drugs — is essentially unknown in humans. Furthermore, information on the developmental changes in transporter expression in animals is mainly restricted to the transport of nutrients (i.e., SGLT1, GLUT2, PEPT1) rather than drugs (Funk *et al.*, 2012). Coordinated efforts to increase the knowledge base in this area would contribute to better treatment options and new effective medications for children. An international network, the International Transporter Consortium (ITC), consisting of academic, industrial, and regulatory scientists, has recently been formed to focus on defining the role of transporters in drug disposition, particularly pertaining to the development of drugs (Zamek-Gliszczynski *et al.*, 2012). An equivalent consortium does not exist in Canada; however, results from specific ongoing trials can contribute to the body of knowledge on pediatric pharmacodynamics (e.g., promising investigations involving drug transporters and methadone toxicity in infants in Toronto and London, Ontario (M. Rieder, personal communication, 2013)).

A great number of developmental changes take place between birth and adolescence, and the effects of these cannot be accounted for by pediatric investigations that do not obtain data across all age groups. These changes are also non-linear in nature, and can progress at varying speeds for different individuals. Because levels of systemic exposure vary following drug administration

to children at different stages of development (e.g., exposure in a newborn will differ from that of an older child), thorough investigations that cover the full continuum of development are needed to gain a complete picture of the impact of age-related physiological changes on pediatric drug pharmacokinetics. However, such investigations are mostly lacking. A recent analysis found that only 24% of the 1,081 ongoing trials in children under 12 years of age and registered in the WHO International Clinical Trials Registry Platform were collecting pharmacokinetic data (Viergever *et al.*, 2011). Researchers concluded that the proportion of ongoing pharmacokinetic research in children worldwide did not seem to adequately address the lack of knowledge in this area. This is also true in Canada, where there are few coordinated efforts to improve the evidence base of pharmacokinetics in children. In the absence of a concerted mandate, individual studies can contribute to the body of knowledge in pediatric pharmacokinetics but can only go so far in improving the evidence base. Moreover, for certain pediatric sub-specialties (e.g., adolescent medicine, developmental pediatrics, neonatology), the insufficient number of residents training in Canada is expected to result in a shortage of qualified personnel to develop these individual studies (Piedboeuf *et al.*, 2012). This is particularly poignant for pediatric clinical pharmacology. In 2012, there were no residency training spots filled for this subspecialty in Canada (CaRMS, 2012).

Finally, inadequate collection of pediatric pharmacokinetic data during the earlier stages of drug investigation can negatively impact subsequent safety and efficacy trials, particularly those that are unsuccessful. Without dose–exposure information, over a wide dose range, it is difficult to determine whether lack of efficacy was caused by inadequate exposure (a pharmacokinetics issue) or differences in the drug response pathway (a pharmacodynamics issue) (Benjamin *et al.*, 2008).

The study of developmental pharmacodynamics has received considerably less attention in the past decades than developmental pharmacokinetics, and there is a general lack of pediatric data and documentation of age effects for pharmacodynamics. The development of many important drug receptors in children has not been described, and some of the developmental pharmacodynamic information being used by prescribers is from animal rather than human trials (Mulla, 2010), a situation less than ideal. More pharmacodynamic data would be useful in understanding age-specific differences and informing the development of effective drugs for children, especially newborns (Tayman *et al.*, 2011), as animal studies suggest that many receptors are maximally expressed shortly after birth (Funk *et al.*, 2012).

3.6.2 Pharmacogenomics and Pharmacogenetics

Much of pharmacogenomic and pharmacogenetic evidence is developed using adult populations, making it difficult to translate this knowledge into appropriate clinical guidance for children. However, a number of approaches to gathering pharmacogenomic and pharmacogenetic data in children are emerging. To recognize well-characterized cases of ADRs and link them to genetic variants, pharmacogenomic investigations are typically conducted with data acquired from both drug safety surveillance and genome-wide association studies (GWAS). This information can also be obtained from more targeted investigations using panels designed to study the genes most likely to be relevant (Carleton, 2010).

GWAS aim to identify new therapeutic targets and predict genetic associations with drug responses (Neville *et al.*, 2011). Some examples of GWAS that have been completed for disorders in children include those for Kawasaki disease, acute lymphoblastic leukemia, early-onset asthma, and pediatric inflammatory bowel disease (Neville *et al.*, 2011). While these approaches have been promising, many challenges are associated with GWAS-based research. Looking for statistical significance in a study in which tens of thousands of genes are being examined requires considerable expertise in statistical genetics to extract meaningful signals from background noise (Martin *et al.*, 2009). Another issue — common to all genetic studies but especially relevant in the case of GWAS-based approaches — is the need for replication of results and functional validation to help inform the biology and underlying mechanisms of the effects in question (Stranger *et al.*, 2011). This is essential if, for example, one wishes to develop an intervention or concurrent therapy approach. In this light, targeted investigations are more likely to produce results germane to known mechanisms, albeit with much less ability to detect previously unknown associations. Examples of targeted investigations include the identification of genetic variants associated with cisplatin-induced hearing loss among children with cancer (Ross *et al.*, 2009; Pussegoda *et al.*, 2013). A combination of further GWAS and targeted investigations that focus on children are needed to continue to build this important evidence base.

Networks such as the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) have been formed to help acquire pharmacogenomic data in children. CPNDS is a pan-Canadian network of clinicians originally in 10 — and now expanded to 12 — pediatric teaching hospitals across Canada (Carleton *et al.*, 2009; CPNDS, 2012). The role of the network is to evaluate ADRs and the specific genetic variations that can help to predict them. For example, CPNDS studies of codeine-induced mortality in breastfed infants have led to changes in

prescribing information and public health warnings about codeine-containing products in the United States and Canada (Carleton, 2010). This initiative is discussed in more detail in Section 6.4.3.

Despite their promise in helping to elucidate variability in drug response, pharmacogenomic and pharmacogenetic investigations also pose a number of challenges. There are important and complex ethical issues associated with trials that gather genetic data in children. Researchers must obtain consent from parents or guardians for children's participation in any genetic study, and specifically for obtaining biological samples, even if the study is long-term, analyzing risk of adverse events in the future when the child has grown to adulthood. In addition, there are a number of technical obstacles, such as practical problems with obtaining biological samples (see Chapter 5 for more discussion on practical challenges in conducting pediatric research). As well, many surveillance systems identifying adverse drug events are based on voluntary submissions and contain few reports, which often translates into insufficient data to undertake a proper investigation (see Chapter 6 for more discussion of monitoring systems). Researchers also often lack matched controls needed to determine genetic differences; many controls are taken from adult populations and other studies that may not be directly comparable to children (Carleton, 2010).

Recent research has focused on changes in genetic expression or phenotype resulting from mechanisms distinct from the genetic sequence. Many of these changes appear to be due to DNA methylation or histone modification, which can change gene expression without changing the basic genetic coding (often termed as *epigenetic* changes) (Zilbauer, 2013). For example, emerging work suggests that differences in DNA methylation are important for fetal growth and development (Banister *et al.*, 2011). However, epigenetics is a relatively new field, and the clinical implications for drug therapy in children remain largely unexplored. As an example, much of the genetic research in developmental biology currently being conducted is in animal models. Extending this work to children will be important to demonstrate how these changes impact clinically relevant outcomes, including response to drug therapy. Genotype and phenotype concordance is also difficult to study on a wide scale; existing studies have been conducted in adults and therefore do not reflect genotype–phenotype differences in developing children. Furthermore, although several studies have identified associations between gene variants and drug exposure or response phenotypes in children, dosing guidelines based on this information are currently lacking. To address this gap, the Clinical Pharmacogenetics Implementation Consortium is working to establish guidelines that will allow translation of genetic test results into prescribing decisions for specific drugs.

Integration of pharmacogenomics into clinical care will require a standard process for connecting specific genotypes to phenotypes and finally to clinical recommendations (Caudle *et al.*, 2014).

3.7 CHAPTER SUMMARY

From a clinical pharmacology perspective, the evidence clearly shows that children are not just little adults. As children develop, they experience a number of significant developmental changes that impact how their bodies deal with medications and how, in turn, medications affect their bodies. These changes render children's response to medications different from that of adults and can also translate into variable drug response across different stages of development (e.g., the response of a newborn will differ from that of an older child).

Even though developmental changes occur from conception to adolescence, the most dramatic age-related physiological changes take place during the first year of life and these populations are most often neglected in studies. However, new methods for collecting biological specimens and analyzing small samples are enhancing the feasibility of performing studies in newborns and infants. These developmental changes occur in a non-linear fashion and do not all proceed at the same rate. At the same time, a number of aspects associated with individuals' underlying genetic make-up can affect these developmental changes to further account for variability in drug response. There is some variation and even contradiction between pharmacokinetic processes (e.g., increased volume of distribution for water-soluble drugs in newborns should decrease drug concentration, while at the same time immature hepatic metabolism in the newborn should also increase drug concentration). However, generally speaking the evidence does suggest that pre-term newborns, term newborns, and young infants have immature hepatic metabolism and immature renal excretion and thus need a lower absolute dose of a medication than adults to avoid toxicity, whereas toddlers and children have faster drug clearance (normalized for body weight) compared with adults and thus need relatively higher weight-based doses to avoid therapeutic failure. In contrast, pharmacokinetic knowledge gleaned from adults is more easily transferable to adolescents.

Despite these revelations, there is still a general lack of pharmacokinetic, pharmacodynamic, and pharmacogenomic information about children, particularly in pre-term and term newborns and in young infants. In the cases of pharmacodynamics, genetics, and personalized medicines research, this gap is even more pronounced given that they are relatively new fields and the clinical implications for drug therapy in children remain largely unexplored.

To ensure effective and high-quality care options and to avoid adverse events, these combined factors should be considered when developing drugs for children and when prescribing and administering medications to this population.

M&S represent an emerging method that harnesses information from developmental pharmacokinetics and pharmacodynamics to predict drug exposure and response, thereby helping to plan pediatric dosing studies and analyze data. Individual studies and trials will continue to contribute to this body of knowledge; however, large-scale, coordinated, and concerted efforts to increase the knowledge base in these fields of study hold more promise for contributing to better treatment options and the development of new effective medications for children. These efforts could include promoting and supporting a coordinated agenda that values multiple forms of research in children; supporting multi-centre studies and research networks that build a diverse set of evidence and maximize the research strengths that exist across jurisdictions; and encouraging the documentation (e.g., a pharmacokinetic databank) and synthesis of available knowledge to maximize the use of information and reduce duplication and burden in future research.

4

Formulating and Administering Children's Medications

- **Making Medications that Children Can and Will Take**
- **Adherence to Medication Regimen**
- **Creating the Prescribed Medication Dose**
- **Forms, Delivery Routes, and Devices**
- **Addressing Knowledge Gaps in Medication Formulations, Forms, and Delivery Devices**
- **Chapter Summary**

4 Formulating and Administering Children's Medications

Key Findings

- Many medications given to children have no commercially available, age-appropriate forms and formulations, resulting in manipulation of dosage forms designed for adults. Lack of appropriate forms and formulations of drugs for children can lead to increased risk of error, exposure to unsafe medication components, lack of adherence, and therapeutic failure.
- Excipients, medication ingredients other than the active pharmaceutical ingredients, have been associated with toxicity, allergic reactions, and intolerances in children; some can also affect drug bioavailability. Choice of excipients is therefore critical in formulating drugs for children.
- The availability of suitable pediatric forms and formulations is critical for ensuring the accurate and easily adjusted dosage of a medication and ultimately for successful treatment of children. In the absence of suitable pediatric forms and formulations, proper guidance and standardization in extemporaneous formulation preparation can improve efficacy and safety.
- Developing formulations that appeal to children's preferences for appearance, taste, smell, and texture can impact adherence and quality of care.
- While past pediatric drug development has focused primarily on the use of liquids, the future of drug development involves dissolvable tablets, minitables, drug-device combinations, and other novel forms of drug delivery that allow for more accurate, flexible, and acceptable administration of drugs.
- Internationally, a range of work is underway to develop clear and transferable evidence about excipients, palatability, delivery devices, dispensing, and age-appropriate formulations. Many of these initiatives are unique partnerships among academia, clinical settings, industry, and regulators and point to the importance of both collaborating across sectors and sharing information to improve safety and efficacy of medications for children.

4.1 MAKING MEDICATIONS THAT CHILDREN CAN AND WILL TAKE

As described in Chapter 3 and Figure 3.1, a number of unique developmental factors as well as numerous patient-specific factors affect children's responses to medications. These factors must be considered during the development of therapeutic products. The unique characteristics of children similarly inform

the options for formulating and administering medications. *Formulation* is the term denoting the combination of an active pharmaceutical ingredient(s) (API) with other non-active constituents — termed *excipients* — to create a medication. *Form* refers to the overall physical configuration of a medication (e.g., tablet, powder, capsule, or liquid). The formulation and form of a drug impact its efficacy and safety by ensuring that the drug is delivered at the appropriate dose and to the appropriate site of action; they can also affect bioavailability (discussed in Sections 3.2.1 and 4.3.1). The accuracy of the dose, the effect of excipients, the palatability of the drug and its packaging, and an appropriate delivery route and device (e.g., inhaler or syringe) to administer the drug are particularly important to consider.

This chapter explores this variety of considerations and the challenges in creating appropriate forms and formulations for children. Beyond questions about safety and efficacy, considerations related to forms and formulations are a significant part of dealing with the challenges that affect the overall acceptability of drugs to children and their adherence to a treatment protocol, including in clinical trials. Appropriate acceptability ensures that children receive timely, accurate, and properly administered doses of medications.

4.2 ADHERENCE TO MEDICATION REGIMEN

In addition to the role of the prescriber in determining an appropriate medication and dosing regimen for an individual patient, the delivery of effective care involves *adherence*,¹⁷ defined as the extent to which the patient's behaviour matches the prescriber's agreed recommendations (Haynes *et al.*, 1979). In children, adherence extends to the behaviour of the parent or caregiver to properly administer medications to newborns, infants, and children according to the prescribed schedule, dose, and delivery route. Failure to do so can have significant impacts on quality of care and response to therapy. For adolescents, who may administer their own medications, emotional and social changes may translate into difficulties in adhering to prescribed regimens, especially in the case of chronic disease. Understanding these challenges and their effects on quality of care can help with the monitoring and design of interventions to improve medication adherence.

17 The term *compliance* is often used to describe the extent to which a patient's behaviour matches the prescriber's recommendations; however, the use of this term has declined because it implies a lack of patient involvement. The term *adherence* has been adopted as an alternative because of its emphasis on the patient's role in determining appropriate treatments that are in agreement with the prescriber. *Concordance*, a more recent term used predominantly in the United Kingdom, focuses on an agreement between a clinician and a patient about whether and how medicines are to be taken. The agreement incorporates the views of the clinician while respecting the beliefs and wishes of the patient (Horne *et al.*, 2005).

Patient adherence to a prescribed dosage regimen can affect treatment outcomes for both acute and chronic medical conditions. For children and adolescents with chronic conditions, non-adherence to a prescribed regimen is considered the single greatest cause of treatment failure (Quittner *et al.*, 2008). Poor adherence can mean that the patient does not recover or experience relief from symptoms, which may result in long-term damage. Poor adherence may also cause the prescriber to believe the medication is ineffective and subject the patient to unnecessary diagnostic tests or changes in dosage. Conversely, improved adherence can lead to increased effectiveness of medical treatments (Horne *et al.*, 2005; Haynes *et al.*, 2008). Poor adherence during clinical trials can be detrimental not only for the patient being treated, but also for future patients of medications on trial; it can contribute to inconsistent results, lack of approval, or incorrect indications of dose and frequency (Tebbi, 1993). Similarly, in the case of antibiotics, poor adherence can also lead to the growth of antimicrobial-resistant strains, which can affect whole populations (Pritchard *et al.*, 2003; Baguley *et al.*, 2012).

A prescribed treatment can indicate the dose, frequency, duration, and timing of the administration of a medication. Given the variety of factors to which a patient must adhere to comply with the prescribed treatment, there are a similar variety of avenues through which a patient could stray, affecting quality of care (Quittner *et al.*, 2008). Although it can vary based on a number of factors (e.g., disease complexity), adherence rates for infants, children, and youth have been reported as being between 25 and 60%, and most commonly below 50%, with adolescents typically having the lowest adherence depending on disease and treatment (Costello *et al.*, 2004; Quittner *et al.*, 2008; Fredericks & Dore-Sütes, 2010).

Non-adherence is defined as situations “when the failure to comply is sufficient to interfere appreciably with achieving the therapeutic goal” (O’Hanrahan & O’Malley, 1981). It can arise from either intentional or unintentional behaviour, and can result from many factors on the caregiver’s or adolescent patient’s part, such as forgetfulness, omission of doses, lack of information, emotional factors including those associated with development, financial constraints, negative side-effects, lack of access to medication, lack of disease–state knowledge, or lack of understanding of immediate and long-term consequences (La Greca *et al.*, 2003; Bell *et al.*, 2007; Bullington *et al.*, 2007). Additional prescribing-related factors may also contribute to non-adherence, such as the prescription of multiple medications and complex regimens, failure to explain the benefits and side-effects of treatment, a lack of consideration of a patient’s lifestyle or the cost of medicines, and an overall weak relationship with the patient (Bell *et al.*, 2007). Adolescents may specifically face additional factors such as changing relationships within the family, issues of self-concept, desire to exert autonomy,

and depression (Dunbar & Waszak, 1990). Similarly, infants and children may specifically face challenges with the form or formulation of the drug. Some children may be unable to swallow pills or capsules or may refuse or be averse to the flavours or textures of medications (Mirochnick, 2000).

With this range of challenges in mind, it is important to explore the factors involved in delivering appropriate medications and doses to children at all ages. As stated by Tuleu and Breitreutz (2012), “a medicine the child refuses to take has no bioavailability.” The rest of this chapter explores these ideas, focusing on the evidence for creating an efficacious and safe medication that will actually be taken by children once on the market.

4.3 CREATING THE PRESCRIBED MEDICATION DOSE

As children grow, the effective dose range for any medication may change — within a very narrow window, in some circumstances — in relation to their size (i.e., weight, height, body surface area) and development. Quality care for children therefore relies on the availability of medications in a range of forms to deliver accurate doses that can be easily adjusted to account for these changing requirements (Nunn & Williams, 2005). Many children, especially those younger than seven years, cannot reliably swallow large solid medications, making liquid forms popular and desirable (Standing & Tuleu, 2005; EMA, 2006a). However, many medications have no suitable or commercially available liquid forms, which leaves pharmacists to manipulate existing forms. The requirement for a range of forms that can address children's dynamic needs should be reflected in the available forms of industrially prepared medications for children.

4.3.1 Manipulation of Medications and Bioavailability of Active Pharmaceutical Ingredients

Both the form and formulation of a medication can impact the bioavailability of the API. The chemical composition of a pharmaceutical ingredient may require it to be produced in a certain form, such as a tablet rather than a liquid, to preserve its therapeutic potential. However, this can be problematic for young children who are generally unable to swallow large pills. In addition, the dose may need to be adjusted to accommodate the child's size and state of development. Therefore, it is common practice to rely on *extemporaneous* formulations in pediatrics — medications that have been manipulated by pharmacists to produce suitable forms for children when no appropriate commercial form is available (Brion *et al.*, 2003). The manipulation may consist of crushing tablets or opening capsules and dissolving or suspending

the medication in a liquid excipient to produce oral formulations in various doses. Extemporaneous formulations also include cutting tablets into smaller segments to obtain appropriately sized doses (Brion *et al.*, 2003).

Manipulation of the original form of a medication can alter its bioavailability, although the extent of this change is usually unknown. For example, studies of antiretroviral drug tablets used in children to treat HIV/AIDS suggest that drugs could have different levels of effectiveness when taken whole or crushed. A small study compared the level of drug exposure of whole and crushed antiretroviral lopinavir/ritonavir (Kaletra[®]) tablets administered to 12 patients aged between 10 and 16 years (Best *et al.*, 2011). Results indicated that systemic drug exposure of both lopinavir and ritonavir was reduced by approximately 45% in patients who received a crushed form of the drug compared to those who received whole tablets. These results suggest that an unknown higher dose of the drug might need to be administered to children taking the crushed form to achieve the same therapeutic concentration, along with increased monitoring to ensure safety and efficacy. As such, the crushed form is not recommended in practice (Best *et al.*, 2011). This example highlights the importance of developing appropriate forms of medication for children, and the potential effects on quality of care when they are not available. The study also highlights that manipulations of the commercially prepared form can change bioavailability in ways not necessarily studied or reported during the clinical trial phase and thus can impact the generalizability of the results of any trial.

The shelf-life and storage of medications are also important for both practical purposes and quality of care when determining an optimal children's form (Nunn & Williams, 2005). For instance, while liquids are generally preferable to tablets for infants, liquid formulations usually have a shorter shelf-life, often require refrigeration, are associated with dose accuracy problems, may have an unpleasant taste, and may include more excipients to improve the taste and preserve the stability of the API (Standing & Tuleu, 2005). Many excipients have not been tested in younger children, and could have side-effects (see Section 4.3.2).

Dosing and calculation errors have been shown to be more common in children than in adults (Lesar, 1998; Kozer *et al.*, 2006b; Crouch *et al.*, 2009), with an incidence rate ranging between 4 and 30%, depending on the definition of medication error and the detection approach (IOM, 2007). Studies have shown that the most common medication errors in children relate to confused units of measure or dispensing errors (Crouch *et al.*, 2009; Doherty & Mc Donnell, 2012). However, errors may occur anywhere during prescribing, transcribing, preparation of extemporaneous formulation, or administration.

A common type of error is a prescribed or administered dose ten-fold higher or lower than the recommended dose because of calculation errors or transcription errors (e.g., confusion about the placement of decimals or use of incorrect units (Kozer *et al.*, 2006a)). Ten-fold errors are more often associated with toxicity and death than other types of dosing errors in children. One investigation using data reported to U.S. Poison Control indicated that the majority of ten-fold errors occur in infants (Crouch *et al.*, 2009). A Canadian analysis of voluntary safety-reporting data at the Hospital for Sick Children in Toronto reported that morphine was the most frequently reported drug and opioids in general were the most frequently reported drug class with a ten-fold error (Doherty & Mc Donnell, 2012).

Dosing and calculation errors occur in children for several reasons: more medications are used off-label and therefore lack standard dosing recommendations; many medication forms must be manipulated to adjust for the weight or surface area of a child, which necessitates calculations that are subject to human error and which may create confusion when age- and weight-based recommendations are conflicting; and clinical decisions may not take into account age-dependant pharmacokinetic data (Kozer *et al.*, 2006a). Outside of a clinical setting, children are often reliant on caregivers to administer a dose, and the chance of error may increase with the number of caregivers (e.g., parents, grandparents, child care staff) and care settings (e.g., primary residence, residence of extended family members, daycare).

In addition to calculation errors, extemporaneous formulations add a risk of inaccuracy and increased variability that occurs when medicines are not prepared commercially. For example, tacrolimus is a first-line immunosuppressant drug for pediatric solid organ transplantation for which no commercial pediatric formulation is available (except in Japan). The adult capsule needs to be manipulated in order to provide an oral suspension for young recipients. In one study evaluating the concentration of 11 tacrolimus oral suspensions prepared by local retail drug stores for nine pediatric solid organ transplant recipients, tacrolimus concentration in two suspensions from two liver transplant patients was less than one-tenth of the expected concentration. In one patient, whole blood tacrolimus concentration fell well below the therapeutic range and clinical signs of rejection were present (Lapeyraque *et al.*, 2009). Although based on a small number of patients, this example highlights the potential risks associated with manipulation of drugs and reinforces the need for suitable commercially available forms and formulations for children. This would reduce the need for manipulation and would therefore reduce errors and improve efficacy and safety. In addition, when appropriate pediatric formulations are lacking and health care professionals are required to prepare extemporaneous formulations, they would benefit from evidence-based guidance for manipulation of medicines.

4.3.2 Choosing the Right Excipients

Excipients have an effect on the manufacturing, consistency, stability, sterility, and volume of a medication and therefore its ease of administration; they enable the delivery of the API to the site of action and affect therapeutic stability and preservation as well as taste, appearance, and aroma (Fabiano *et al.*, 2011). Previously considered inactive and generally tested only in the adult population, some excipients have been associated with toxicity, allergic reactions, and intolerances in children (Fabiano *et al.*, 2011). Although excipients are widely used in medications for children, the effects of most excipients during human development are unknown (Ivanovska *et al.*, 2013). This poses a challenge to produce formulations that can deliver safe, effective, and quality treatments.

The selection of excipients for medical formulations depends on the properties of the API to be delivered as well as the pediatric product profile and the desired bioavailability. Individual excipients can vary in their functional role depending on the grade, type, and source selected for each particular therapeutic formulation (Mills, 2007). Adding, changing, or deleting a single excipient in a medicinal formulation can unintentionally affect the bioavailability of an active ingredient (Tuleu & Breitkreutz, 2012). For example, replacing sugar with a sugar substitute in a liquid formulation can reduce its intestinal permeability and the rate that an active ingredient is absorbed through the intestinal lining (Chen *et al.*, 2007). Sugars are commonly used in oral liquid dose forms as sweetening agents, and previous investigations have revealed the varying effects of different sugars on gastrointestinal transit (Chen *et al.*, 2007). A recent paper investigated the effects of sorbitol, a sugar substitute that does not cause dental caries, and sucrose on the bioequivalence of ranitidine, a gastrointestinal drug with high intestinal permeability, and metoprolol, a cardiovascular drug with a low intestinal permeability (Chen *et al.*, 2007). The total amount of ranitidine that reached blood circulation (a measure of the dose delivered to the body) was reduced by 45% in a sorbitol formulation compared to a sucrose formulation; the same effect was not seen with metoprolol. The majority of effects on bioavailability caused by changes in excipients are undetected unless bioequivalence studies are performed, which is rarely the case in children, creating potential safety and efficacy issues.

Excipients that are generally considered safe and inert in adults can have toxic effects in children. For example, benzyl alcohol and propylene glycol are commonly used to preserve and dissolve API, respectively (Shehab *et al.*, 2009). The amount of these excipients administered in individual doses is not acutely toxic. However, in newborn infants, who have immature metabolic systems, these excipients can accumulate following repeated or continuous dosing, eventually becoming toxic (Shehab *et al.*, 2009; Whittaker *et al.*, 2009). Propylene glycol has been documented to cause hyperosmolarity (high blood glucose levels), neurotoxicity, and seizures in newborn infants (Breitkreutz & Boos, 2007). Benzyl alcohol has been linked to intraventricular hemorrhage, metabolic acidosis, neurotoxicity, and increased mortality in newborns, especially those with low birth weights (Menon *et al.*, 1984; Breitkreutz & Boos, 2007). Despite these findings and documented contraindications, formulations containing these two excipients are still administered to newborn infants and infants (Shehab *et al.*, 2009). A recent study that examined infant exposure to propylene glycol and benzyl alcohol over a one-year period found that, among the more than 1,000 infants under the age of 28 days who were admitted to neonatal and pediatric intensive care units of a single institution, about 40% received medications containing either benzyl alcohol or propylene glycol (Shehab *et al.*, 2009). For patients who received treatment via continuous infusion, the median dose received was between 21 and 180 times the acceptable daily doses of benzyl alcohol and propylene glycol, respectively.

The above study by Shehab *et al.* (2009) highlights the need to determine the clinical consequences associated with excipient exposure in infants. The toxicity of excipients can also be affected by the route of administration (e.g., intravenous versus oral administration) and the form of the drug (e.g., solid versus liquid formulations) (Breitkreutz & Boos, 2007; Whittaker *et al.*, 2009). There may be elevated toxicological risks in children for a number of excipients that have not been fully investigated, and infants are the population with fewest data.

Table 4.1 describes some of the examples of excipients used in liquid and tablet oral forms and their purpose in a medication formulation, where risks in children and existing regulations have been identified.

Table 4.1
Select Excipients and Identified Safety Risks in Children

Tablet Excipients	Purpose	Examples	Documented Safety Issues in Children	Regulations
Diluents (fillers and bulking agents)	To make weight and size practical for ingestion, to aid in manufacturing.	Lactose, maltodextrin, mannitol, microcrystalline cellulose, sorbitol, starch, sucrose, xylitol.	<ul style="list-style-type: none"> • Congenital lactose intolerance occurs in newborns and varies among ethnic groups. • Sucrose and sorbitol are toxic in newborns with hereditary fructose intolerance; sucrose is poorly tolerated in sucrose–isomaltase deficiency. 	<ul style="list-style-type: none"> • Quantity in over-the-counter drugs limited under U.S. legislation.
Lubricants	To aid in manufacturing and prevent powders from sticking to manufacturing equipment.	Magnesium stearate, talc, stearic acid.	<ul style="list-style-type: none"> • Talc is generally nontoxic when ingested but inhalation can cause respiratory distress in children. 	<ul style="list-style-type: none"> • None found.
Liquid Excipients	Purpose	Examples	Documented Safety Issues in Children	Regulations
Solvents/ Cosolvents	Vehicle to aid in liquid formulation.	Water, propylene glycol, glycerol, castor oil, peanut oil, ethanol.	<ul style="list-style-type: none"> • Ethanol toxicity causes intoxication, lethargy, respiratory depression. • Propylene glycol is linked to CNS adverse events in newborn infants, and to hyperosmolality. 	<ul style="list-style-type: none"> • Ethanol: In U.S., maximum permitted quantities in over-the-counter products: 0.5% for children <6 years; 5% for children 6–12 years; 10% for children >12 years. • Propylene glycol: WHO arbitrary limit in adults is 25 mg/kg/day.

continued on next page

Liquid Excipients	Purpose	Examples	Documented Safety Issues in Children	Regulations
Preservatives	To prevent contamination.	Sodium benzoate, benzoic acid, butylated hydroxy anisole, potassium sorbate, sorbic acid, parabens, thimerosal, benzyl ethanol.	<ul style="list-style-type: none"> Thimerosal can cause mercury toxicity in CNS at high doses. Benzyl alcohol is potentially toxic in newborns (especially with large cumulative doses as seen with continuous infusions). Parabens: Human data lacking; animal data suggest low levels safe in humans ≥ 2 years; newborns anticipated to have less developed propylparaben-metabolizing enzymes so safe levels unknown. Sodium benzoate can cause skin reactions (e.g. hives) in children. 	<ul style="list-style-type: none"> Thimerosal in pediatric vaccines banned by FDA in 1999 and is discouraged by the EMA.
Antioxidants	To control the oxidation of the API.	BHT, BHA, ascorbic acid, propyl gallate.	<ul style="list-style-type: none"> A small outbreak of methemoglobinemia in infants caused by BHA, BHT, and propyl gallate has been reported. 	<ul style="list-style-type: none"> None found.
Wetting Agents	To aid wetting and dispersion of a hydrophobic active ingredient; preservative, or antioxidant.	Polysorbates, sorbitan esters.	<ul style="list-style-type: none"> Polysorbates 20 and 80 have been associated with serious adverse events including liver/kidney failure and death in newborns. 	<ul style="list-style-type: none"> None found.
Sweetening/Flavouring Agents	To make therapeutic more palatable, mask unpleasant flavours or odours.	Sorbitol, saccharin, aspartame, acesulfame, peppermint, butterscotch.	<ul style="list-style-type: none"> Aspartame harmful for those with phenylketonuria. Sorbitol can cause osmotic diarrhea. Sucrose/dextrose cause dental caries. 	<ul style="list-style-type: none"> None found.

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Liquid Excipients	Purpose	Examples	Documented Safety Issues in Children	Regulations
Humectants	To prevent evaporation and condensation on neck of bottle, which can cause cap to lock.	Propylene glycol, glycerol, sorbitol.	<ul style="list-style-type: none"> Sorbitol can cause osmotic diarrhea. Glycerol: High concentrations and volumes may cause mucositis or diarrhea. 	<ul style="list-style-type: none"> None found.
Plasticizing Agents	To increase palatability by sealing off drug inside capsule or tablet; to provide resistance to degradation in stomach before absorption in intestines; to control drug release in modified-release preparations.	Phthalates (DBP, DEP, PVAP, CAP, HPMCP).	<ul style="list-style-type: none"> DBP has been classified by the European Commission as toxic for reproduction on the basis of non-clinical data. 	<ul style="list-style-type: none"> In E.U., all devices containing DBP are to be labelled and the manufacturers must justify presence in devices intended for use in children, and pregnant or nursing women. The EMA has developed exposure guidelines for DBP, DEP, and PVAP to limit their use.
Colouring Agents	To aid in patient acceptance and add complementary colour to flavoured medications.	Azo dyes (e.g., tartrazine).	<ul style="list-style-type: none"> Controversy concerning safety profile of tartrazine, which has been linked to hives and bronchoconstriction, primarily in people who already suffer from recurrent hives or asthma, respectively. 	<ul style="list-style-type: none"> In U.S., drugs containing tartrazine are labelled with a warning. In E.U., tartrazine is discouraged in pediatric formulations.

Data Source: Rosensweig (1975); Nitzan *et al.* (1979); Ali *et al.* (1998); IOM (2001); Breikreutz and Boos (2007); Elhkim *et al.* (2007); Mills (2007); Strickley *et al.* (2008); Shehab *et al.* (2009); Nunn (2011); Mori *et al.* (2012); EMA (2013b, 2013e); Ivanowska *et al.* (2013)

Abbreviations: BHT (butylated hydroxytoluene); BHA (butylated hydroxyanisole); DBP (dibutyl phthalate); DEP (diethyl phthalate); PVAP (polyvinyl acetate phthalate); CAP (cellulose acetate phthalate); HPMCP (hydroxypropyl methylcellulose acetate phthalate)

4.3.3 Palatability of the Medicine

Palatability is the term used to refer to the overall acceptance of the taste, after-taste, smell, dose volume, size, and texture of a medicine to be inhaled or administered orally (WHO, 2012). Given that the most common route of administration for children is oral (Walsh *et al.*, 2011), palatability is important to consider when developing medicines. Parents have indicated the importance of palatability, especially taste, in antibiotic therapy, as the most important factor following safety and efficacy (Matsui, 2007). A number of palatability elements should be considered when formulating the taste, smell, texture, and colour of medications, including the chemical and physical parameters of the drug itself.

Avoiding unusual flavours and complex taste mixtures can increase the probability that a formulation will be accepted (EMA, 2006a). The taste preferences and sensory experiences of children differ from those of adults; for example, children have a preference for sweet flavours and are more averse to bitter tastes (EMA, 2006a; Ventura & Mennella, 2011). Most small-molecule drugs are bitter-tasting and therefore require some degree of taste masking. Liquids can have flavours added, and tablets can be coated in masking agents. Cultural factors, age and gender, genetic differences, the medical condition being treated, and the need to balance unappealing flavours of the API can impact the palatability of the medication (EMA, 2006a). These factors are listed in Table 4.2 along with examples and descriptions of some of the considerations that influence palatability when determining the optimal flavour profile for children's medicines (EMA, 2006a).

Because of differences in adults' and children's taste, palatability studies should be performed in children and use techniques such as recording spontaneous verbal judgments or facial expressions (Matsui, 2007). However, techniques such as this may be problematic in young children, so additional analysis with an electronic taste device can be beneficial (Gupta *et al.*, 2010). For example, electronic tongues, such as the commercially available *αAstree* electronic tongue or Insent[®] taste testing system, use sensor membranes and electrochemical techniques to detect single substances and complex mixtures in medication formulations (Woertz *et al.*, 2011).

Smell and texture also impact the palatability of medications administered orally, intranasally, and topically. The design of intranasally administered medications should take into account the effects of both smell and taste, as medication can drip down the back of the throat and taste bad (Scadding, 2009). Texture can play an important role in palatability in children but has received little attention in pharmaceutical development (EMA, 2006a).

Table 4.2

Factors Affecting Flavour Choices for Pediatric Formulations

Factor	Consideration	Examples
Cultural Factor	Different geographical regions and cultures prefer different flavours.	<ul style="list-style-type: none"> • Europeans prefer citrus and red berries. • Scandinavians prefer licorice. • Americans prefer bubble gum, grape, and cherry. • Japanese prefer less intense sweetness.
Age and Gender	Different age groups and genders have different levels of sensitivity for some flavours.	<ul style="list-style-type: none"> • 4–12-year-old girls are more sensitive to sweet and salty flavours than boys.
Genetic Differences in Taste Appreciation	Selection of formulation within individual flavours should appeal to the majority of patients.	<ul style="list-style-type: none"> • There are both genetic and age components to aversion to bitterness.
Association with Medical Conditions	Some flavours are more commonly associated with certain symptoms or illnesses.	<ul style="list-style-type: none"> • Berry, banana, and caramel flavours for medications to treat pain, fever, allergy, or infection. • Citrus or peppermint flavours for antacids to treat indigestion. • Blackcurrant, lemon, lime, mandarin, and orange for multivitamins.
Balance of Unappealing Flavour	Need to know the taste profile of a formulation before flavours are added to be able to mask it.	<ul style="list-style-type: none"> • Cherry and citrus balance acidic flavours. • Caramel and vanilla balance salty flavours.

Data Source: EMA (2006a); Mennella and Beauchamp (2008); Lipchock *et al.* (2012)

The colour and appearance of medical formulations can also influence palatability and overall acceptability. Colour and shape can also play a role in reducing accidental administration errors by clearly differentiating medications from one another (EMA, 2012a). Although brightly coloured preparations are preferred for children and can be used to trigger recognition of a flavour, many colouring agents are not globally accepted due to reports of their various side-effects in children (EMA, 2006a). A variety of studies have been published with conclusions that support (Bateman *et al.*, 2004; McCann *et al.*, 2007), negate (Mattes & Gittelman, 1981), or are unclear (Nigg *et al.*, 2012) about the effect of artificial dyes on hyperactivity. Other reported side-effects include gastrointestinal intolerance (e.g., abdominal pain, indigestion, vomiting) and dermatological reactions (Scadding, 2009). The use of artificial colouring agents is therefore generally avoided unless necessary, but more research is required to clarify the potential for dyes to produce various side-effects in children at different stages of development. The EMA guidelines for colouring agents indicate that the necessity for inclusion of a colouring agent in a medical formulation must be addressed along with the selection of a particular colouring agent (EMA, 2012a).

Developing formulations that appeal to children's preferences for appearance, taste, smell, and texture can impact adherence and quality of care. Safety and ethical considerations are also involved in making medications appear too similar to candy, increasing the risk of overdose and sending the wrong message that medicines are not to be taken seriously. Therefore, when developing forms and formulations for children, researchers and industry face significant challenges in defining all of these considerations and understanding how each can be addressed in ethically and safely.

4.3.4 Packaging the Formulated Medicine

Medication packaging plays the dual role of preserving the medication to maintain its effectiveness and indicating the basic market for which it is intended. Given the significant impact that packaging has on the effective use of a therapy, and the unique considerations for children, strategies for ensuring the safe and accurate administration of medications and guidelines for appropriate standards are important. Clear marking and the use of bright colours and pictures on the packaging of a medication can help to indicate its appropriateness for children and reduce the accidental administration of adult formulations.

Packaging also protects formulations from the environment (e.g., water, air, contamination, and oxidative degradation) and, through child-resistant containers or wrapping, protects the contents from unsupervised access (Mills, 2010). Manufacturers must ensure that all packaging, including delivery devices, that comes in contact with the medication is clean and safe.

4.4 FORMS, DELIVERY ROUTES, AND DEVICES

A range of medical formulation options are needed to address the changing requirements of different developmental stages. These options may involve delivery devices that enable more accurate dosing via the appropriate delivery route. A variety of new devices have been developed that offer benefits over traditional delivery methods. However, the range of products on the market can vary in terms of accuracy and consistency and can have different benefits and challenges depending on the targeted stage of development. In addition, any medication delivery device design must consider that parents or caregivers may be required to accurately administer the correct dose for their child.

Many pediatric therapeutic administration devices are available for different routes of administration; the most common are types of measuring spoons and cups, syringes, inhalers, and dropper bottles. (For a detailed review of different devices including their advantages and disadvantages, see Walsh *et al.* (2011)).

Some specific delivery routes are considered more appropriate based on age, development, and medical condition, but the accuracy of the delivery devices associated with these delivery routes remains a challenge. For example, liquid oral medications are more commonly used for infants, toddlers, and young children because dosing can be flexible and large tablets or capsules need not be swallowed (Walsh *et al.*, 2011). However, spoons are the most common delivery device (Walsh *et al.*, 2011), and many are inaccurate and not standardized measures (EMA, 2006a). For young children in particular, spoons are difficult to control and may spill. Syringes may be more accurate and appropriate for drugs with a narrow therapeutic index and can more easily facilitate dose adjustments (EMA, 2006a; Walsh *et al.*, 2011).

Similarly, many pulmonary devices (e.g., pressurized metered-dose inhalers) require a greater level of coordination, not yet present in infants and young children, to ensure that breaths are taken at the right moment to receive an appropriate dose of medication. Other devices (e.g., soft mist inhaler, dry powder inhaler) and accessory devices (e.g., valved holding chamber) can reduce the coordination required, limiting deposition of the drug in the upper airways and ensuring proper deposition in the lungs (Walsh *et al.*, 2011). Accuracy and flexibility remain key challenges for many traditional delivery devices, and novel delivery devices and forms are required to address these issues.

4.4.1 Novel Delivery Devices and Forms

A number of new devices and forms that aim to improve the accuracy and ease of delivery are in the development stages. Many different approaches to the oral delivery route have been developed specifically for children. For example, an oral dose can be administered to infants through a modified nipple attached to a pacifier or through a MediBottle® that incorporates an oral dispenser (Walsh *et al.*, 2011). Some manufacturers have developed therapeutic pastes that form when a spoon containing a powdered therapeutic dose is submerged in water (Walsh *et al.*, 2011) (see Figure 4.1A). Existing forms can also be modified and made more accurate and effective for infants and young children. Minitablets are smaller versions of tablets that are easier for patients who have difficulty swallowing large tablets and capsules. Minitablets also offer more dosing flexibility. Although data are generally limited about the acceptability of tablet or capsule sizes in different age groups, very young children have difficulty swallowing large tablets and can choke (EMA, 2012a). A recent investigation of the adherence to 2 mm minitables versus liquid formulations in children aged from six months to six years found that acceptance of the tablets was

either equal to or greater than that of the liquid, even for those aged 6 to 12 months (Spomer *et al.*, 2012) (see Figure 4.1B). Furthermore, children were more likely to refuse to take the liquid than the minitab. This may be advantageous in the case of pharmaceutical ingredients that are more easily or stably formulated in tablet form.

Additional modifications to the oral tablet form are dispersible and orodispersible tablets (ODTs). Dispersible tablets dissolve readily in water or another liquid. Orodispersible tablets are uncoated tablets containing excipients such as crospovidone, croscarmellose sodium, sodium alginate, and acrylic acid derivatives, termed *super disintegrants*, that cause the tablet to disintegrate in the mouth in about 60 seconds (Dey & Maiti, 2010). Similar forms include films and wafers. They offer an advantage for young children and are gaining in popularity since they avoid the need to swallow whole tablets. They are also stable, easy to manufacture, and not subject to first pass metabolism (i.e., direct absorption in the mouth increases bioavailability) (Dey & Maiti, 2010). An example of a novel oral delivery device is Clarosip[®], which uses a flavoured straw to deliver clarithromycin antibiotic micropellets (Ivanovska *et al.*, 2013). In addition, medicated lollipops, chewing gum, and gummy bears have been designed as appealing medication delivery devices for children (Ivanovska *et al.*, 2013). Although these novel approaches may improve adherence, there are safety and ethical concerns when medicines appear too much like candy (e.g., increased risk of overdose). For pre-term and term infants, prenatal vaccination and transfer of antibodies through breastmilk are potential delivery routes being explored for effects in children (see Box 4.1).

Novel pulmonary delivery devices for children include various inhaler adapter chambers (Walsh *et al.*, 2011) (see Figure 4.1C). The benefit of these devices is that they limit the inhalation flow rate and provide visual and audio stimulation (e.g., bright colours, funny faces, whistle noises) to improve appeal. Other pulmonary delivery forms include nanoparticle dosage forms, which are better adapted to reach more distal airways and are therefore more effective, but still have poor pulmonary deposition efficiency (Giacchia *et al.*, 2012).

Needle-free devices for the parenteral (injection or infusion) delivery of insulin, vaccines, and growth hormones have also been developed to reduce fear and increase safety (Walsh *et al.*, 2011).

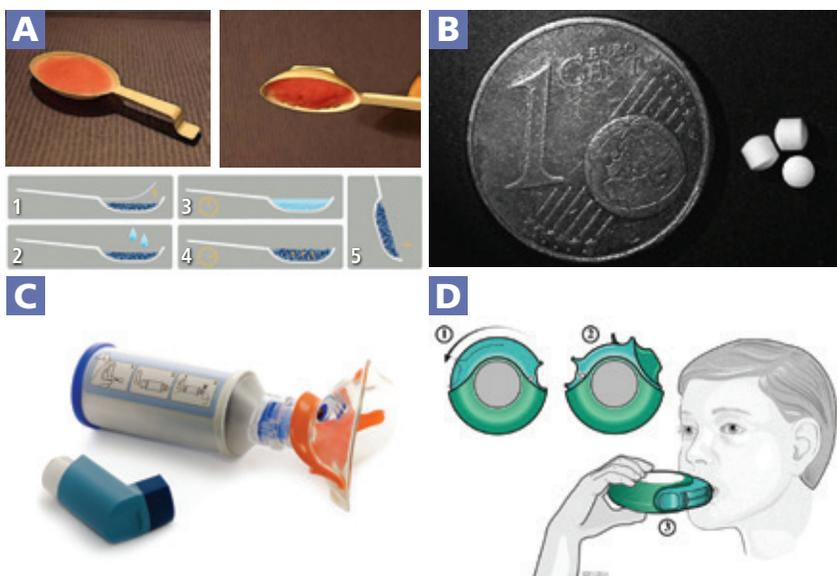
Novel delivery devices for children increasingly bring together the device and the medication; such combination products are defined by the U.S. FDA as comprising two or more regulated components (e.g., drug, device, biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity (Mills, 2010). An example of such a combination is a dry powder inhaler, in which the pharmaceutical ingredient is preloaded in the delivery device for the patient (see Figure 4.1D).

Box 4.1

Intentional Transfer of Antibodies from Mothers to Newborns, Infants, and Toddlers

Recently vaccinated mothers can use breastfeeding as a method of delivering potentially protective antibodies to newborn infants who are too young to be vaccinated (Maertens *et al.*, 2014). In general, live vaccines that contain viable pathogens (e.g., measles, mumps, rubella) may pose a theoretical risk to pregnant and breastfeeding mothers; however, inactivated vaccines (e.g., diphtheria, tetanus, pertussis) show no increased risk and offer potential disease immunity for both mother and child (Hubka & Wisner, 2011). Although evidence suggests that vaccination during pregnancy leads to higher levels of pathogen-specific antibodies in breast milk (Halperin *et al.*, 2011), very little data are available on the protection provided by these antibodies. Thus far, a protective effect has been most clearly shown for infants of influenza-vaccinated (inactivated vaccine) mothers (Maertens *et al.*, 2014).

Recommendations for the vaccination of pregnant and breastfeeding mothers are made by the U.S. Centers for Disease Control and Prevention (CDC, 2013) and Health Canada. Health Canada recognizes the theoretical risk of live vaccines but states that “in general, routinely recommended vaccines may be safely administered to breastfeeding women” and recommends immunization for breastfeeding women who have not received all recommended adult immunizations (PHAC, 2012a). Transmission of protection from mother to child is not specifically mentioned in the Canadian Immunization Guide (PHAC, 2012a). However, one Canadian study has clearly documented this benefit in animals (Elahi *et al.*, 2006). The transmission of drugs from breastfeeding mother to child can be ethically challenging to study; hence a general lack of information in the field.



Courtesy of (A) Egalet, Inc., (B) Spomer *et al.* (2012) (BMJ Publishing Group), (C) Vitaly PaKulov (6999800) Dreamstime.com, (D) Cleveland Clinic (2014)

Figure 4.1

Novel Delivery Devices and Forms

Researchers are developing a number of new devices or forms to improve the accuracy and ease of delivery of drugs to children. The figure shows a few examples: (A) submergible spoons developed by Parvulet®, (B) 2 mm minitablets, (C) inhaler adapter chamber, (D) dry powder inhaler combination delivery device.

4.5 ADDRESSING KNOWLEDGE GAPS IN MEDICATION FORMULATIONS, FORMS, AND DELIVERY DEVICES

4.5.1 Gaps in Formulations

The unique requirements of children's formulations present challenges in drug development; however, some initiatives have begun to address these challenges.

The U.S. Pediatric Formulation Initiative (PFI) was formed as a project of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) in 2005 to identify the issues and challenges in developing formulations for children, to raise awareness, and to facilitate preparation of safe and effective medicines for children. The Economics Working Group within the PFI was established to identify the economic barriers hampering the creation of cost-effective and appropriately formulated products for off-label pediatric drugs, propose mechanisms to create such products, and ensure their distribution and availability (Milne & Bruss, 2008).

The European Paediatric Formulation Initiative (EuPFI) is another example of a large-scale consortium working to improve knowledge about development of formulations and better medications for children. EuPFI is a unique collaboration between academia, clinical settings, industry, and regulators that draws on the expertise of relevant clinical pharmacology sectors to improve the knowledge base. In addition, EuPFI regularly collaborates with the equivalent U.S.–based initiative (EuPFI, 2014). The initiative is working to develop evidence related to excipients, palatability, delivery devices, dispensing, and age-appropriate formulations. Although no such formulation initiative exists in Canada, there is great potential for similar work and opportunities for collaboration with these established international efforts.

The best scenario for treating children involves commercially available age-appropriate forms and formulations with known bioavailability based on adequate bioequivalence studies. In the absence of such formulations, guidance on appropriate form and formulation manipulations would improve efficacy and safety of drugs. To address the continued worldwide need for effective extemporaneous formulations of medications for children (Nahata & Allen Jr, 2008), a recent report from WHO provides some general instructions on manipulating adult dosage forms and advice on administering medicines for children (Nunn, 2011). The report refers many decisions on rounding of dose or substitution of drugs for more suitable forms to the professional judgment of the pharmacist (Nunn, 2011).

To support the future development of guidelines on the manipulation of dosage forms for children, a project to develop a systematic approach to reviewing the literature and evidence on drug manipulations — the Pediatric Formulations Platform — was initiated in 2009 as an inter-agency agreement between the U.S. FDA and the NICHD (NIH, 2012b). The first report from this initiative outlines an Oral Formulations Platform, which attempts to provide baseline information for the development of new formulations of new and existing APIs. It lists 382 products that have been approved for use in children and classifies the dissolution, solubility, and intestinal permeability characteristics of each (NICHD & FDA, 2011). Coordinated initiatives such as this will help to improve knowledge on effective forms and formulations of currently approved and future drugs for children.

Although there is a paucity of data about the effects of excipients on children, there are a number of challenges associated with conducting trials to assess the extent of this risk. A recent trial conducted on newborn infants to examine the safety of propylene glycol examined differences between formulations of the same compound; the availability of techniques to measure excipients accurately; inaccuracies in isolating the pharmacokinetics of an excipient from

disease symptoms or accumulation factors; and difficulties in determining useful pharmacodynamic outcome variables, since existing indicators may be based on adult values (Kulo *et al.*, 2012). The lack of trial experience on the safety of excipients made it difficult to meet these challenges and develop solutions — a situation likely to be common to other excipient trials in children.

The EMA recently released a concept paper that considered the role of excipients in medications for children (EMA, 2012f). In addition, the EMA reviewed the European Commission guidelines on excipients (European Commission, 2003) to include effects in children, and developed a *Guideline on Pharmaceutical Development of Medicines for Paediatric Use* that includes considerations in the evaluation of the safety profile of excipients in pediatric formulations for specific target age groups (EMA, 2012a). The guideline gives examples of questions that must be answered to verify the safety of an excipient, and the corresponding paths of investigation. This could serve as a helpful framework for evaluating excipient doses and safety.

The Database of Safety and Toxicity of Excipients for Pediatrics (STEP database) in Europe aims to address the worldwide gap in knowledge through collaborations between the Pediatric Formulation Initiatives in the European Union and the United States. The STEP database contains detailed reviews of excipients used in pediatric formulations, identifies knowledge gaps and safety issues early in the development process, and reduces delays and duplication of efforts (Salunke *et al.*, 2012). In Canada there is no repository of excipient information, although Health Canada publishes an index of non-medicinal ingredient nomenclature to encourage uniformity and avoid confusion (HC, 1996). There is an opportunity to expand resources such as this to include information on toxicity and safety and to collaborate with international jurisdictions currently undertaking initiatives with similar goals.

Although palatability has been identified as an important factor in children, formal studies that examine the relationship between palatability and adherence are lacking (Matsui, 2007; Giacoia *et al.*, 2012). These studies are not part of the standard regulatory requirements set by the ICH. In addition, the need to understand ethnic and regional variations has been identified but not fully documented, as have the influences of environment and family support in taste preferences and adherence for all stages of development (Giacoia *et al.*, 2012). Evaluations of taste in adults may not apply to children for the reasons described, and youth trials have some specific challenges. For example, children aged over four years are considered able to participate in taste trials to qualitatively assess palatability. However, most trials limit tasting to four drugs during a session to avoid the risk of taste confusion or fatigue (EMA, 2006a).

Taste tests of medications that are administered over the long term are not feasible, as most trials investigate preferences following one or a few doses. Moreover, the information available from taste trials with children is also restricted to an overall reaction to the medication rather than a differentiation between taste and texture (Matsui, 2007). The effects of colour on taste preference have likewise not been well studied (Matsui, 2007), and possible side-effects of artificial colourings also need to be investigated (Nigg *et al.*, 2012).

At its second workshop on pediatric formulations in 2012, the U.S. PFI specified that regulatory requirements in the United States are limited in their discussion of palatability. Unpleasant sensory properties such as bitter flavours are not recognized until a medication reaches the first stage of clinical trials (Giacoaia *et al.*, 2012). This is an obstacle in the development process for palatable medications for children. Although testing in potential consumers is considered the best way to assess palatability, other methods such as animal models, taste sensors, or electronic tongues can be used to quantitatively assess taste and smell characteristics (Lorenz *et al.*, 2009; Gupta *et al.*, 2010).

4.5.2 Gaps in Forms and Delivery Devices

Determining the appropriate form for children at different ages and stages of development requires some assessment. A number of considerations factor into the decision of whether tablets or capsules are appropriate forms for a young child. The EMA has developed a matrix that combines information on age groups, routes of administration, and dosage forms to reflect the variability in children's ability to swallow solid dose forms (EMA, 2006a). For example, the matrix considers tablets as potentially acceptable (although not preferred) from age three, with increased acceptability after age six (Ivanovska *et al.*, 2013). Many other dosage forms are also highlighted and coded in a way that prioritizes acceptability across various age ranges.

Ultimately, given some of the unique challenges for the pediatric population in terms of therapy, novel devices that can assist in consistent and accurate delivery are in demand. As part of the U.S. PFI, a working group of academics, industry, and government representatives was created in 2011 to develop and prioritize goals for new technologies and drug delivery systems. While past drug development has focused primarily on liquids, the future of drug development clearly involves dissolvable tablets, minitables, and other novel forms of drug delivery that allow for more accurate and acceptable administration of drugs (Giacoaia *et al.*, 2012). In Canada, there is an opportunity for similar collaboration involving academia, clinicians, industry, and regulators working together to improve innovation and advance knowledge in this field. Significant developments could then be shared with other successful international ventures.

The rising popularity of combination products on the market creates a number of unique regulatory challenges as this type of product may be assessed by different regulatory pathways depending on its primary mode of action. In addition, combination products must be thoroughly evaluated before made available for pediatric users. The U.S. FDA has compiled a number of guidance documents for combination products on its website that detail approval and manufacturing requirements. Health Canada also has a policy on drug/device combination products that took effect in early 2006. Under the policy, combination products are subject to either the *Medical Devices Regulations* or the *Food and Drug Regulations*, according to the principal mechanism of action by which the claimed effect or purpose is achieved. The policy is meant to serve as an interim mechanism in the regulatory scheme until the *Food and Drugs Act*, *Food and Drug Regulations*, and *Medical Devices Regulations* can be amended to provide a regulatory framework more appropriate for new therapeutic products that are difficult to classify under the current system (HC, 2005a).

This gap in the regulatory scheme creates a disincentive to sponsors for the development of novel medical combination products because approval is not managed under one set of regulations. The Therapeutic Products Directorate and the Biologics Genetic Therapies Directorate have recognized this gap (HC, 2005a). The policy document released in 2005 states that the “Directorates believe that the risks associated with a combination product can be managed appropriately under one set of regulations” (HC, 2005a). The document further states that a new approach would “harmonize regulatory requirements with both the United States and European Union and would assist in the development of mutual recognition agreements with those jurisdictions” (HC, 2005a). Follow-up along these lines would facilitate the development of novel combination devices for children and their release in the Canadian market.

4.6 CHAPTER SUMMARY

A number of developmental factors unique to children should be considered when formulating and delivering medications. Without appropriate forms and formulations of medications to meet the needs of children there is an increased risk of error, exposure to unsafe medication components, lack of adherence, and therapeutic failure. Manipulation of the original form of a medication can alter its bioavailability and affect quality of care. Manipulations of the commercially prepared form can also change bioavailability in ways not necessarily studied during the clinical trial phase and thus can impact the generalizability of the results of any trial. Quality care for children therefore relies on the availability of medications in a range of forms to ensure the delivery of a medication is accurate, and so that doses of medication can be easily adjusted to account for changing requirements related to development. 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 form and formulation manipulations would improve efficacy and safety of drugs. Specific, detailed, and evidence-based recipes for preparing extemporaneous formulations should be provided to encourage standardization of this process.

Although excipients are widely used today in medications for children, the effects of most excipients during human development are unknown and many excipients generally considered safe and inert in adults can have toxic effects in children. Adding, changing, or deleting a single excipient in a medicinal formulation can unintentionally affect the bioavailability of an active ingredient, which can go largely undetected without adequate bioequivalence studies. Given that the most common route of administration in children is oral, palatability is an important consideration for the development of any children's medicine. Developing formulations that appeal to children's preferences for appearance, taste, smell, and texture can impact adherence and quality of care.

Some specific delivery routes are considered more appropriate for different ages, stages of development, and medical conditions. The use of liquid oral medications is more common for infants, toddlers, and young children because it allows flexible dosing and avoids the need to swallow large tablets or capsules. However, achieving an accurate and standardized dose with liquid medications is a challenge. A number of new delivery devices have been recently developed to target routes of delivery that are appropriate for children, and their widespread use could increase quality of care. The range of products on the market can vary in accuracy and consistency and can have different benefits and challenges depending on the targeted stage of development. However, while past drug development has focused primarily on the use of liquids, the future of development is likely to emphasize dissolvable tablets, minitables, drug-device combinations, and other novel forms of delivery that allow for more accurate and acceptable administration of drugs and dosing adjustment and flexibility.

In Canada there is no repository or centralized source of known information about acceptable and safe forms and formulations for children. However, internationally there is a range of work underway to develop clear and transferable evidence related to excipients, palatability, delivery devices, dispensing, and age-appropriate formulations. Many of these initiatives are unique partnerships among academia, clinical settings, industry, and regulators and point to the importance of collaborating across sectors and sharing of information to improve efficacy and safety of medications for children. Beyond questions of efficacy and safety, forms and formulations are a significant part of dealing with

the challenges that affect the overall acceptability of drugs to children. There are many opportunities for Canada to join international efforts to ensure that ultimately children receive timely, accurate, and properly administered doses of medications.

5

Improving Current Approaches to Pediatric Efficacy Studies

- Studying Efficacy in Children
- How Efficacy Trials Are Incorporated into Medicine Development
- Challenges of Studying Drug Efficacy in Children: An Overview
- Randomized Controlled Trials
- Modifying the Design of RCTs to Improve Their Suitability for Pediatric Research
- Analysis Techniques that Support Pediatric Studies
- Challenges in Carrying out Efficacy Studies in Children
- Chapter Summary

5 Improving Current Approaches to Pediatric Efficacy Studies

Key Findings

- 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.
- For testing the clinical efficacy of medications, randomized controlled trials (RCTs) provide the strongest evidence and are least susceptible to bias. RCTs are feasible for evaluating the efficacy of a medication in children in most situations, although flexibility and modifications may be required.
- Challenges of conducting RCTs in children include the need for flexibility in the design of classic parallel group RCTs, perceived acceptability issues with inclusion of children in RCTs (particularly those that involve a placebo control), and recruitment of adequate patient numbers (especially in the case of rare diseases).
- RCTs may be modified to improve their suitability for studying the efficacy of pediatric medications by using sequential or adaptive/flexible designs, active comparators rather than placebos, and multicentre studies to address the challenges of studies in these patients.
- Innovative techniques, such as repeated n-of-1 trials, Bayesian analysis, and extrapolation, may offer support for pediatric RCTs by helping to maximize the value of small data sets and previous studies.
- Recent guidelines address ethical challenges in pediatric trials, and research groups are standardizing age ranges and appropriate outcome measures for RCTs. Fostering a culture that supports pediatric drug efficacy studies and providing guidance on the use of various design approaches would further expand the evidence base for child health.

5.1 STUDYING EFFICACY IN CHILDREN

Regulators require evidence about the efficacy and safety of each proposed treatment for drug registration and market authorization. This evidence typically comes from clinical trials, which provide information that can translate into clear guidance (for regulators and practitioners) on how a drug can be used to treat children. However, as discussed in Chapter 2, many medicines given to children have not been adequately studied in that population, and are prescribed off-label, in the absence of robust scientific evidence. The lack of pediatric clinical trials stems from a range of challenges. This chapter focuses on best research

practices for studying the efficacy of drugs in children by suggesting methods for dealing with these challenges. It first discusses randomized controlled trials (RCTs), and the perceived difficulties of using this approach for pediatric clinical research. It then reviews some RCT modifications and analysis techniques that address specific pediatric research concerns. It concludes with a discussion of some general challenges and corresponding solutions in pediatric efficacy studies that are broadly applicable to many study types. Research practices and challenges related to pediatric safety studies are described in Chapter 6.

5.2 HOW EFFICACY TRIALS ARE INCORPORATED INTO MEDICINE DEVELOPMENT

An overview of the drug development process is shown in Figure 5.1. A new product is first tested *in vitro* (outside of a living organism) and in animals for preliminary information about efficacy, safety, and toxicity. For products that perform well during this pre-clinical phase, the next step is applying to Health Canada's Health Products and Food Branch (HPFB) for permission to carry out clinical trials with human subjects (HC, 2006). Clinical testing begins with a Phase I trial, which explores the pharmacokinetic processes — absorption, distribution, metabolism, and elimination — involved when taking the drug (discussed in Chapter 3) and the safety profile of a new product using a wide range of drug doses. Phase I trials may use healthy volunteers or individuals with the condition for which the product has been developed. Including healthy children in Phase I research is limited to specific circumstances (see Section 5.7.2).

In Phase II trials, a narrower, potentially therapeutic dose range is investigated. This phase provides preliminary efficacy data, often using surrogate outcomes¹⁸ that indicate whether the product can halt progression or alleviate symptoms in patients with the disease the drug is intended to treat. From Phase I and II studies, dose-response data define the lower limit for product efficacy and the upper limit beyond which no additional improvement is measured or unacceptable toxicity is observed.

18 In clinical trials, surrogate outcomes (such as changes in physiological variables or biological measures) are frequently used in place of clinical outcomes (events that directly change the health of an individual in a meaningful way, such as prevention of death or morbidity or enhancement in quality of life) (Yaster *et al.*, 2012). Surrogate outcomes are often faster or cheaper to assess, but can be misleading if they are not carefully validated to ensure that they are able to predict clinical outcomes based on scientific evidence. According to Hirschfeld (2010), “patients who have a positive outcome based on a poor surrogate may not experience true clinical benefit” if, for example, the surrogate is statistically correlated but not causally associated with the clinical outcome.

Phase III trials are more demanding in terms of their sample size, measurement of efficacy (quantified using actual clinical endpoints such as disease progression), and timeframe (to measure effects of sustained use) (Yaster *et al.*, 2012). Following promising clinical trials, manufacturers may file a New Drug Submission with HPFB (HC, 2006). Once a drug is registered and granted market authorization, any adverse events are tracked through various methods of pharmacovigilance (see Chapter 6). In addition to monitoring safety, continued evaluation of drugs is important for measuring their *effectiveness*, which refers to their benefit under normal conditions of use (i.e., real-world circumstances). In contrast, the benefit of a drug measured within the ideal, controlled setting of a clinical trial is referred to as its *efficacy* (Artlett *et al.*, 2005).

The step-wise process described above is rarely followed when researching drugs for children. Children are less likely to be involved in Phase I and II studies, which means that larger Phase III pediatric trials may be developed based primarily on adult data and some pediatric pharmacokinetic studies (Iyasu & Murphy, 2007). In certain cases, pediatric efficacy trials do not start until a drug has already been marketed for adults and thus may actually be considered as post-market efficacy trials by the time they are conducted in children. To avoid confusion, the Panel defines pre- and post-marketing drug studies in the following way:

- *Pre-marketing studies*: Efficacy or safety studies conducted before a drug has been approved for any indication (i.e., the drug has not yet been marketed for the treatment of any disease or any age group).
- *Post-marketing studies*: Efficacy or safety studies conducted after a drug has been approved for at least one indication in one age group. These studies may be related to the approved indication (e.g., studies that investigate a drug's long-term harms, benefits, and optimal use) or they may test efficacy and safety in new sub-populations such as children (FDA, 2013c). As discussed in Chapter 6, post-marketing studies are the main method for investigating possible adverse drug reactions in the wider, real-world population.

Whether they occur before or after market authorization, drug efficacy studies are usually clinical trials (as opposed to observational studies). However, this is not always the case, as discussed below. In the post-marketing setting, a scenario highly relevant to children is the use of an efficacy study to test a new age group or sub-population, a new formulation, or a new dosing schedule. In the latter two cases, an established, effective therapy (an *active comparator* — see Section 5.5.2) is often compared to the new formulation or dosing schedule to determine whether these modifications render the new treatment more effective than the established one (Scheifele *et al.*, 2007; Faye *et al.*, 2012).

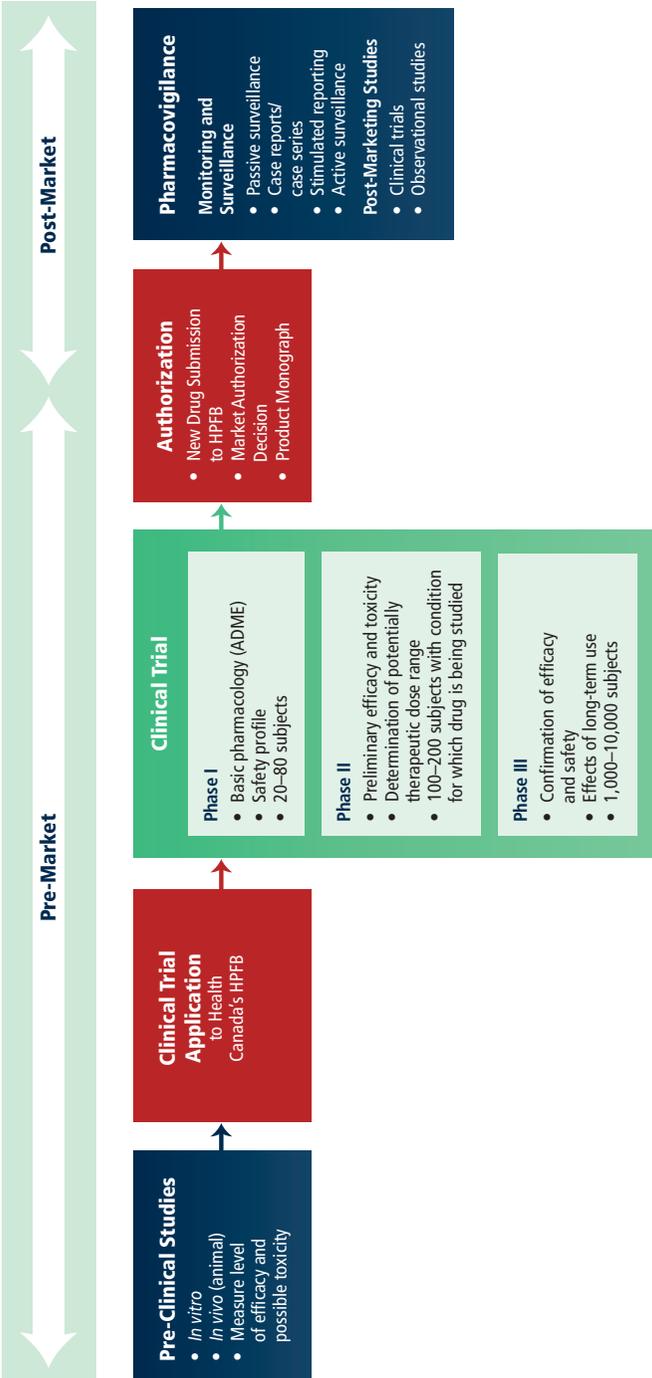


Figure 5.1

The Process for Developing Medicines in Canada

For adults, efficacy is primarily studied before a drug is approved for sale (market authorization). This pre-market testing involves four phases of studies, starting with pre-clinical studies (not in humans), which are followed by three numbered phases in humans. Following the regulator's marketing authorization decision, the manufacturer may conduct post-marketing studies to determine, for example, efficacy within sub-populations such as children or in combinations with other drugs.

An additional type of post-marketing analysis uses an approach more common for detecting adverse drug reactions (discussed in Chapter 6). This approach relies on monitoring initiatives and subsequent observational studies to continue collecting and analyzing information on efficacy post-marketing. A necessary element for this methodology is the maintenance of a database network that allows different types of health information from an individual to be accessed centrally. Manitoba Health maintains such a system; it involves several electronic databases (e.g., the Drug Program Information Network and the Manitoba Immunization Monitoring System or MIMS) that can be linked using a unique health services number assigned to each individual. The databases were harnessed to monitor the efficacy of the H1N1 influenza vaccine by linking information on the immunization status of individuals from the MIMS with specimen testing results from the province's public health laboratory (the Cadham Provincial Laboratory). By examining the H1N1 vaccination status of those who tested positive for influenza and those who tested negative, the study determined that the vaccine was highly effective in individuals aged 6 to 35 months and 3 to 49 years, and less effective in those who were over age 50 or immunocompromised (Mahmud *et al.*, 2011).

Since the goal of vaccinations is to produce long-term immunity, other types of vaccine-specific concerns studied post-market include decline in efficacy over time or declining efficacy as a result of combining vaccinations. For example, Tomovici *et al.* (2012) performed a multi-centre RCT to evaluate antibody persistence after a single booster dose of Tdap (tetanus, diphtheria, acellular pertussis) vaccine in adolescents and adults. Before boosting, many participants lacked detectable antibodies to pertussis antigens, suggesting that they were susceptible to pertussis (whooping cough) due to waning immunity after childhood immunization. After boosting, most participants were still seropositive for at least one pertussis antigen 10 years later, but levels had waned significantly. Thus, the decline in efficacy of the Tdap vaccine, combined with insufficient coverage rates of booster doses, provide a mechanism for maintaining the pertussis reservoir. This is a significant concern for effectiveness, particularly for young infants, who are more susceptible to morbidity and mortality due to pertussis infection (Tomovici *et al.*, 2012).

An additional efficacy issue may arise with combined vaccines. For example, when a diphtheria, tetanus, and acellular pertussis vaccine was combined with *Haemophilus influenzae* type b (Hib) vaccine, the Hib antibody response induced by the combination vaccine was significantly lower than the response induced by separate administration of the Hib vaccine. However, observational studies showed that the combination vaccine was still able to protect children from Hib-induced disease (Eskola *et al.*, 1999; Denoël *et al.*, 2007).

Collectively, these approaches demonstrate that efficacy data collected post-market continue to be useful for approved drugs. They also emphasize the varied objectives of efficacy studies and the range of methodologies that can be used to meet these varied goals.

5.3 CHALLENGES OF STUDYING DRUG EFFICACY IN CHILDREN: AN OVERVIEW

The study of medication efficacy in children poses some unique challenges (outlined in Figure 5.2). As mentioned, drug efficacy studies are typically clinical trials; therefore, the majority of these challenges relate to conducting RCTs. Before planning a clinical trial, it is useful to consider the available information in order to maximize previous knowledge and reduce any research burden. A systematic review and meta-analysis of prior data (from animals, adults, and children) may reveal that further clinical efficacy studies can be reduced in scope or avoided altogether if data already exist or if extrapolation is possible (see Section 5.6.2).

Even if a clinical trial is required, existing information will likely still be useful for planning the new study. For example, data from previous studies may help researchers decide which patients to enroll in an upcoming trial, particularly for therapies that are highly affected by individual factors that enhance or attenuate treatment efficacy. These factors may be biomarkers, which relate to the probability that an individual may in fact experience a pharmacological effect (e.g., a biomarker that indicates the presence of a receptor for the drug under investigation), or mutations in the genes encoding drug-metabolizing enzymes (see Chapter 3). Consideration of these factors contributes to the eventual goal of clinical drug research, which is to estimate the safety and efficacy of a drug treatment in individual patients, rather than the mean treatment effect in a group of somewhat similar patients with similar conditions. This approach is being used by the Children's Oncology Group (COG) to design clinical protocols with new anti-cancer drugs based on accumulating information. Larger initial trials with broader populations are expected to reveal molecular features (e.g., expression of specific molecules by tumor tissue) associated with particular disease subtypes that respond differently to treatment. Subsequent smaller studies are then completed with therapies targeted toward specific molecular subtypes of the disease (Gajjar *et al.*, 2013; Gamis *et al.*, 2013).

If plans are made to conduct an RCT, a range of challenges must be addressed. Figure 5.2 divides the general challenges of pediatric efficacy studies into four main categories:

- *Ethics*: Many of the ethical concerns of clinical research are amplified in children since they lack the capacity to understand information about harms and benefits of participating in a trial and are therefore not legally competent to provide informed consent (Tri-Council, 2010). However, compared to the 1998 version of Canada’s nationally enforced policy on research ethics — the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Tri-Council, 2005) — the updated version reflects a view more receptive to research with children. For example, it acknowledges that although certain populations, such as children, may have a diminished ability to exercise autonomy (i.e., to “deliberate about a decision and act based on that deliberation”), participation of these populations in research can be “valuable, just and even necessary” if appropriate measures are taken to ensure that they are sufficiently protected (Tri-Council, 2010).
- *Acceptability*: The research community recognizes the importance of including children in clinical pharmacology studies. However, there has sometimes been hesitancy to enroll children due to their vulnerability (Pickler & Martin, 2010), and for this reason they have been excluded from all types of research (Grondin & Glantz, 1994). Over time, this has left children as *therapeutic orphans* (Kodish, 2005; Avard *et al.*, 2009).
- *Rarity*: The number of children afflicted with many pediatric conditions is low, particularly if they are rare diseases or if they affect children of a specific age range.
- *Standardization*: Lack of clear standards and appropriate and validated endpoints for pediatric trials impede their consistent execution, and make it difficult to compare different studies of the same drug.

The above challenges can be applied to pediatric studies in general. These and other challenges also relate specifically to the design requirements of classic parallel group RCTs (see Section 5.4), which may be difficult to meet when studying children. Following a review of RCT design, the remainder of this chapter discusses potential solutions (including trial design modifications, analysis techniques, and clarifications to guidelines) to the challenges of pediatric efficacy studies.

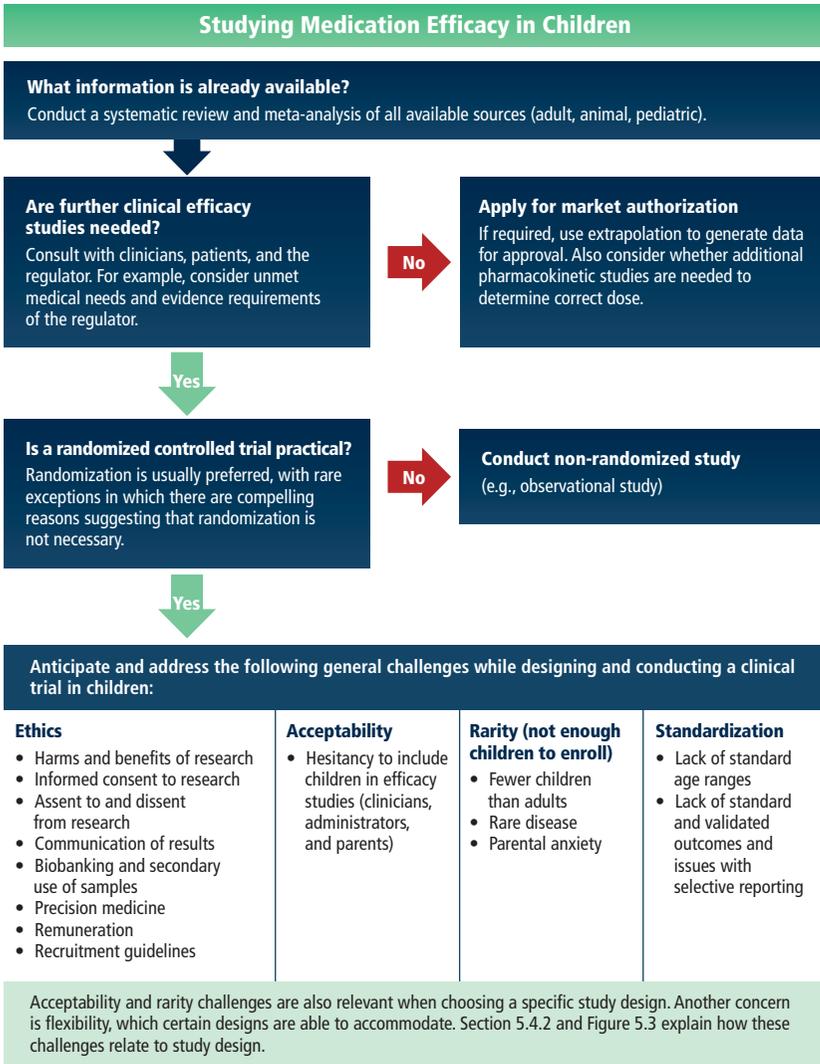


Figure 5.2

Framework for Addressing General Challenges in Pediatric Efficacy Studies

Before planning a pediatric clinical trial, it is useful to consider available information, which may reveal that further clinical studies can be reduced in scope or avoided. If the decision is made to perform an RCT, researchers must address a range of challenges that are specific to trials in children. These challenges fit within the broad categories of ethics, acceptability, rarity (in terms of the number of children available for study), and standardization. Some of these challenges are also relevant when choosing a specific study design (See Figure 5.3).

5.4 RANDOMIZED CONTROLLED TRIALS

The World War II era has been referred to as “the great divide in medical research” (Kaptchuk, 1998). Prior to this period, clinical research relied heavily on human judgment. Eventually, controlled trials became recognized as the preferred method for establishing new therapies (Sacks *et al.*, 1982). At first, randomization of participants to control and treatment groups was not common but was subsequently established as a method for reducing bias, allowing blinding, and producing conditions that were closer to those assumed by statistical tests (Chalmers, 1981). Physicians were initially reluctant to accept the results of RCTs, particularly when the conclusions of these studies differed from their personal opinions. In addition, some considered RCTs unethical, since they involve treating patients based on chance rather than clinical judgment. However, earlier champions of this method recognized that “unconscious bias may distort the outcome of a trial” and when the effect of a treatment is uncertain, RCTs are in fact the most ethical way to conduct research (Chalmers, 1981). In some cases, RCTs have proven that certain treatments, which were expected to be beneficial, were actually ineffective or even harmful. Regulatory agencies now require RCTs for the approval of most new drugs, and they have been used successfully to test therapies for most major diseases (DeMets, 2002).

5.4.1 Basics of Randomized Controlled Trials

In current clinical research, RCTs are first carefully designed to test a hypothesis. Following study planning and ethical approval, RCTs proceed to patient recruitment from among the target population. In a screening phase, information about patients’ baseline clinical conditions is collected and their eligibility for the trial is determined. After they provide written informed consent to signify their voluntary participation, eligible individuals are then randomly assigned to an intervention (e.g., treatment or control), a practice referred to as *randomization*. Random assignment minimizes the possibility that the baseline characteristics of each group will be systematically different (biased) in terms of clinical, demographic, and prognostic factors (Cipriani & Geddes, 2009). The assignment is usually performed by a randomization sequence generated using readily available computer programs or random number tables (Hartling *et al.*, 2012a). A trial that compares treatment and control groups concurrently is referred to as a *parallel group trial* (Cochrane Collaboration, 2013). An additional key aspect of an RCT that can always be implemented is *allocation concealment*, the process to ensure that, from the point the patient is identified as eligible to the point of randomization, there is no way of ascertaining to which group the patient will be assigned.

Another desirable element is *blinding*, which describes the process used to prevent subjects, investigators, and others involved in the trial (e.g., outcome assessors) from being aware of which intervention a patient is receiving. The rationale for blinding is to ensure that all subjects in the various groups in a trial are treated in the same way. The other benefit of blinding is to ensure that outcome assessment is unbiased (Hartling *et al.*, 2012a). Scientific journals often use the term *double-blind*. There is no standard definition for double-blind and it may refer to any combination of blinding (e.g., participants and investigators/clinicians or participants and outcome assessors). Thus, an ideal description of the methodology for a particular RCT includes an explicit description of the blinding procedure (Cipriani *et al.*, 2008).

The final critical issue is to ensure complete follow-up of all patients in a trial; if patients are lost to follow-up or withdraw, the reason and group assignment are noted and a method for analyzing the data from them must be provided. The purpose of randomization, allocation concealment, blinding, and complete follow-up is to avoid bias in clinical trials.

Reduction of Bias by RCTs

Bias (systematic error) is sometimes confused with *imprecision* (random error). An imprecise study may have a rigorous design, but may produce different results each time it is repeated due to a small sample size, use of an outcome measure with low reliability, or other reasons that could be adjusted. In contrast, a biased study has a design flaw that leads to over- or under-estimation of the true intervention effect, and would still produce inconsistent results even if other parameters such as sample size were adequate (Higgins & Altman, 2008; Hartling *et al.*, 2012a). *Confounding* “occurs when the estimate of a measure of association between drug exposure and health status is distorted [biased upwards or downward] by the effect of one or several other variables that are also risk factors for the outcome of interest” (Csizmadi *et al.*, 2005). These variables can influence the relationship between drug exposure and health status (e.g., worsen an adverse response) or may make it challenging to prove that drug exposure had a genuine effect on the outcome.

The design of RCTs prevents various types of bias and confounding. By keeping the baseline characteristics in each group free from systematic differences, randomization helps prevent *confounding by indication*.¹⁹ If researchers are blinded, they are prevented from unconsciously systematically providing a different level of care to patients in different groups (*bias due to co-intervention*). In addition, blinding prevents differential analysis of outcome data between groups (*measurement bias*). Participants can also be affected by lack of blinding. If they discover which treatment they are receiving, it could impact their behaviour and their reporting of subjective symptoms such as pain (also *measurement bias*) (Higgins & Altman, 2008). It is preferable to use relevant, validated, and objective outcomes (e.g., laboratory test results, or all-cause mortality) to protect against bias;²⁰ however, in most situations patient-reported outcomes can be important for measuring the effect of a treatment (Matza *et al.*, 2013).

While an ideal clinical trial would strive to eliminate most potential sources of bias, the degree to which a given type of bias will impact a study and the direction of the bias must be taken into account. For example, if a study has potential biases that are expected to reduce the magnitude of a treatment effect, but the RCT still indicates that the treatment is effective, then the results may be considered valid (Higgins & Altman, 2008). The challenge is that the direction of bias on treatment effect is often unknown. In addition, RCTs can be subject to issues of generalizability that cannot necessarily be controlled by their design. An example is *volunteer bias*, where systematic differences may arise when a sample can include only people who are willing to participate in the study, and who may have exposures or outcomes that differ from those who decline (Jordan *et al.*, 2013).

Risk of Bias in Pediatric RCTs

Hartling *et al.* (2012a) recently reported on three studies that examined the risk of bias in pediatric clinical trials using the Cochrane Risk of Bias tool (Hartling *et al.*, 2009; Crocetti *et al.*, 2010; Hamm *et al.*, 2010). In two of these studies, the overall risk of bias was unclear or high for the majority of trials. Furthermore, these trials had exaggerated treatment effects when compared

19 Without randomization to assign patients to particular treatment groups, those with certain baseline characteristics (e.g., good overall health) may be prescribed treatment A and those with other characteristics (e.g., poor health) may be given treatment B. An observational study may falsely conclude that treatment A leads to a better outcome when patients in this group were already healthier. This is referred to as confounding by indication (Jepsen *et al.*, 2004).

20 The terms used to label different types of bias vary due to differences in terminology between fields of research or subtle distinctions between the situations that these terms describe. For example, *bias* and *confounding* are sometimes distinguished by the fact that bias must be prevented at the design stage but confounding can be reduced during data analysis. However, in practice, this is not always the case, since it may not be possible to obtain a sufficiently accurate estimate of the effect of a given confounder (Csizmadi *et al.*, 2005).

to those at low risk of bias (Hartling *et al.*, 2009; Hamm *et al.*, 2010). Two of the most problematic areas were *sequence generation* (the method for generating a random allocation sequence) and *allocation concealment* (the method for ensuring that the randomization sequence is unknown to participants and those enrolling participants). Thus, the current methodological approaches for pediatric clinical trials may result in trials with a high risk of bias, signalling a need for further research into reasons for these risks and strategies for mitigating them (Hartling *et al.*, 2012a).

Control Groups in RCTs

The major purpose of including a control group for comparison is to discriminate between the effects of an investigational treatment on patient outcomes (e.g., changes in symptoms, signs, or other morbidity) and outcomes caused by other treatments, the disease itself, or the absence of treatment (ICH, 2000b). The FDA and the ICH describe four types of trials with concurrent control groups or *arms* (i.e., parallel group trials): placebo, active comparator, no treatment, and dose-response (ICH, 2000b; FDA, 2010a). The most common and widely recognized type of control is a placebo (Streiner, 2007). *Placebos* are treatments such as pills or injections, that do not contain the test product but appear as identical as possible to the test product in terms of their physical characteristics (ICH, 2000b). Placebo groups are used to differentiate drug effects from *placebo effects* (actual or perceived improvements) and to maintain blinding. They are sometimes referred to as negative controls. RCTs that include a placebo control group are designed to answer the question “does the therapy work?”

An *active comparator* (i.e., a proven therapy that is effective and that is typically the standard of care for the given condition) may be used as a comparator rather than a placebo (Fleming, 2008). RCTs that include an active control group are designed to answer the question “does the therapy work compared to usual care?” Active comparators are discussed further in Section 5.5.2. Trials may also have a *no-treatment control* group. Since no attempt is made to conceal treatment assignments, subjects and investigators are aware of the assignments (lack of blinding), increasing the risk of bias. This design may be useful in situations where blinding is difficult (e.g., treatments with side-effects that are easily identified). *Dose-response* trials include groups receiving different doses of a therapy to determine the most likely dose to result in the desired response, and these trials may also include placebo or active control arms (ICH, 2000b).

5.4.2 Challenges in Choosing a Study Design for Pediatric Research

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 (Shaddy & Denne, 2010; Hartling *et al.*, 2012b). To meet this responsibility, RCTs with a placebo control group are acceptable for children as long as they are justified scientifically and ethically, such as in cases of *equipoise* — a state of genuine uncertainty about the comparative efficacy of the therapy given to each treatment group in a trial (Freedman, 1987). Use of a placebo is justified in some circumstances, such as “when there is no other commonly accepted therapy for the condition,” or when the efficacy or harm-benefit profile of the commonly used drug is in question (Shaddy & Denne, 2010). For an example of a placebo-controlled trial in infants, see Box 5.1.

Box 5.1

A Canadian Strength in Newborn RCTs: Caffeine for Apnea of Prematurity

Pre-term infants commonly experience a condition known as apnea of prematurity, involving pauses in breathing and cessation of respiratory airflow. Clinical interventions for apnea of prematurity include continuous positive airway pressure and drug treatment (Stokowski, 2005). Methylxanthines (e.g., caffeine) have been used for decades to treat this condition and are one of the most commonly prescribed drugs in newborn medicine (Millar & Schmidt, 2004; Conroy & McIntyre, 2005). Despite its widespread usage, a licensed form of caffeine for newborn administration is available only in the United States and Europe (Conroy & McIntyre, 2005; EMA, 2009).

Methylxanthines reduce apnea of prematurity through multiple mechanisms, one of which involves inhibiting adenosine receptors. Adenosine has protective functions in the brain, so once this mechanism was discovered, questions were raised about possible adverse effects of methylxanthines on growth, neurological development, and behaviour. In addition, most of the research on the efficacy of methylxanthines had focused on short-term benefits (Millar & Schmidt, 2004). To address these safety and efficacy concerns, a landmark Canadian-led undertaking, the Caffeine for Apnea of Prematurity (CAP) study, was initiated in 1999 (ClinicalTrials.gov, 2013).

continued on next page

The CAP study is a multi-centre, randomized, placebo-controlled trial, involving participants from Canada, the United States, Australia, Europe, and Israel. Initial results confirmed the short-term benefits of caffeine (earlier discontinuation of positive airway pressure and reduced rate of bronchopulmonary dysplasia, a chronic lung disorder) (Schmidt *et al.*, 2006). Follow-up at a corrected age of 18 to 21 months revealed a reduced incidence of cerebral palsy and cognitive delay in the caffeine-treated infants (Schmidt *et al.*, 2007). By age five, the caffeine group no longer differed from the placebo group in terms of motor or cognitive function, a finding that was partially due to an overall decline in the rate of cognitive impairment from 18 months to 5 years in both groups. A reassuring outcome from this longer-term follow-up was the absence of any adverse effects in the caffeine-treated children (Schmidt *et al.*, 2012). CAP researchers will continue to follow this cohort so that outcomes at age 11 to 12 can be examined. By investigating a practice that was used for decades without adequate safety or efficacy data, CAP researchers have reduced the uncertainty surrounding caffeine treatment for apnea of prematurity, allowing clinicians to prescribe it without fear of long-term adverse effects.

Certain perceived limitations of placebo-arm RCTs (and parallel group RCTs in general) make them seem less appropriate for studying therapeutic products in children than in adults. These limitations can often be overcome, as shown in Europe and the United States, and demonstrated in Box 5.1. Many of these limitations are also relevant for adults, but may be magnified in children.

- *Perceived lack of flexibility*: RCTs are commonly thought to have rigid rules that cannot be changed after the initiation of a trial without invalidating results. In reality, it is not uncommon to modify trial procedures (e.g., eligibility criteria, treatment duration, endpoints) or statistical procedures (e.g., sample size, data analysis methods) as more information about a treatment becomes available after a trial starts (Chow & Chang, 2008). This scenario may occur more often in children since they are less likely to be involved in Phase I and II studies. As a result, a Phase III pediatric trial may be developed with little pediatric-specific information (Iyasu & Murphy, 2007). For example, it may be difficult to predict the sample size that will be necessary to demonstrate a minimally important difference if the given pediatric population has not been previously studied (Van der Lee *et al.*, 2008, 2010; Van der Tweel *et al.*, 2012). In the 1970s, researchers began developing mathematical methods to allow repeated

testing of interim trial data and subsequent modification of parameters such as sample size (Pocock, 1977; O'Brien & Fleming, 1979). These methods have been used in clinical trials for many years (Chow & Chang, 2008). However, there are newer study adaptations that are less well understood and not yet a common part of the RCT planning process (FDA, 2010c).

- *Ethical considerations and perceived lack of acceptability*: Although there are ethical considerations for RCTs in both adult and pediatric trials, these are amplified in trials involving children because of their perceived vulnerability. It may be seen as unethical to assign children to the placebo arm of a trial if equipoise is lacking (Baiardi *et al.*, 2011) or if an effective treatment is available outside of the trial. However, analyses of clinical trials have suggested that new treatments tested in these trials are just as likely to be inferior as they are to be superior to standard treatments (Kumar *et al.*, 2005; Soares *et al.*, 2005). Furthermore, when perceived ethical concerns have been used as reasons not to conduct pediatric research, in some cases children have been unintentionally harmed; many of the medicine-related catastrophes in the 20th century involved children (Saint-Raymond & Brasseur, 2005), and assessment of these medicines in children using RCTs may have revealed their risks. Many researchers recognize that placebo groups are not inherently unethical if they are the most scientific way of assessing efficacy and safety (Saint-Raymond & Brasseur, 2005). However, parents may be hesitant to enroll their children in a trial knowing that they could receive a placebo and not a potentially beneficial treatment, even if this treatment is still in the research stage (Smith *et al.*, 2008). Physicians may be more likely to encourage patients to enroll in trials with active comparators rather than placebos due, in part, to the belief that active comparator trials offer patients a greater opportunity for personal benefit (Halpern *et al.*, 2002).
- *Rarity*: To achieve statistical significance in an RCT, data may be needed from hundreds or possibly thousands of study participants. Target enrollment may be difficult to achieve when studying children because there are fewer children than adults in most countries (World Bank, 2013), and the number of potential participants may be decreased further if the condition is rare or if the disease occurs in a specific age group. Additional reasons for low enrollment include parental anxiety concerning their child's participation in a research protocol (Pickler & Martin, 2010; Dunne *et al.*, 2011), possibly due to fear of invasive monitoring, such as blood testing, and studies with highly specific enrollment requirements, such as a narrow age range.

5.5 MODIFYING THE DESIGN OF RCTS TO IMPROVE THEIR SUITABILITY FOR PEDIATRIC RESEARCH

Various trial modifications can help to address the perceived limitations of RCTs for pediatric efficacy studies. Figure 5.3 provides examples of the types of questions researchers can consider when planning an efficacy study that may deviate from a classic parallel group RCT.²¹ Some of the possible modifications described below generate results with a higher risk of bias, which increases the chance of erroneous conclusions (FDA, 2012b). Others may not increase the risk of bias, but rather limit the types of research questions that can be explored, thus limiting the conclusions that can be drawn from the study. Certain international regulatory agencies, such as the FDA and EMA, generally recognize the caveats that accompany modified designs and the precautions that must be taken when using them but support the application of these approaches for drug approval (EMA, 2012b; FDA, 2012b). However, because the use of these designs for drug approval is not yet standard practice, investigators would benefit from discussing their design with the regulator before conducting a study to ensure that the study will be sufficient to support regulatory approval.

5.5.1 Using Designs that Allow Trial Flexibility

RCTs can be modified to enhance their flexibility in numerous ways, and pediatric researchers may find these modified designs particularly beneficial. The increased flexibility comes from the opportunity to perform analyses on accumulating data as a trial is in progress. These studies can be divided into sequential designs and adaptive (also known as flexible) designs (Vandemeulebroecke, 2008).

Sequential designs can help to increase efficiency and address ethical concerns. Rather than continuing to enroll and randomize children until a pre-determined sample size has been reached, they allow researchers to repeatedly test whether enough information has been collected to determine which intervention is superior. This may enable early stopping of a trial, thereby saving resources, decreasing the number of children that receive an ineffective treatment, and reducing the total number of children needed for the trial (Van der Lee *et al.*, 2008, 2010). Validity can still be maintained without specifying the number and timing of interim analyses before the trial begins (Lan & DeMets, 1983). Once a trial is running, however, sequential designs do not allow any deviations from the original plan, such as an increase in sample size (Vandemeulebroecke, 2008).

21 The Panel acknowledges that there are different types of RCTs but, for ease of categorization, refers to anything other than a parallel group RCT as a *modified RCT*.

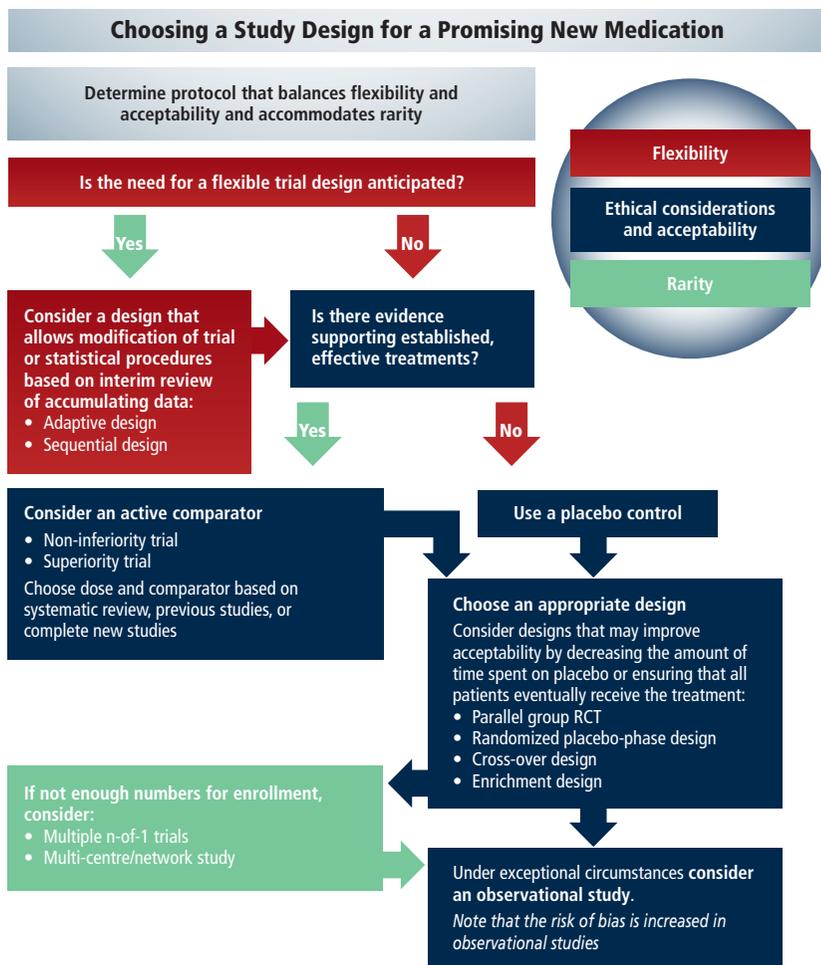


Figure 5.3

Choosing a Design for Studying Efficacy in Children

A classic parallel group RCT can be modified in numerous ways that make it more appropriate for studying drug efficacy in children. Planned interim adjustments based on accumulating data can help to increase the flexibility of the trial. This approach may be particularly useful for children since there is a greater chance that less information will be available before the trial begins. If a known effective treatment is available outside of the trial, an active comparator (rather than a placebo control) may be appropriate. Study designs that decrease the amount of time spent on placebo or ensure that all patients eventually receive the treatment, such as randomized placebo-phase designs (RPPD) or cross-over designs, can help address perceived acceptability concerns from patients, parents, and investigators, thereby enhancing enrollment. If it is difficult to recruit enough patients for a trial (e.g., when studying a rare disease), multi-centre trials and multiple n-of-1 trials are potential solutions. If exceptional circumstances preclude any type of experimental study, an observational study may be considered.

Adaptive designs are essentially a more flexible type of sequential design since they permit trial adaptations based on interim analyses (Vandemeulebroecke, 2008). Once modifications have been made, a new phase of the trial starts. All phases are analyzed separately, and the p -values of each one are combined using a predefined rule (Van der Lee *et al.*, 2008) (see section 5.6.1 for a discussion of p -values). Generally, to ensure validity of results, a detailed protocol for permitting any trial modifications must be made during trial planning; the decision to perform modifications takes place as the trial proceeds and data are analyzed (FDA, 2010c). The FDA emphasizes a critical difference between adaptations based on blinded interim analyses (i.e., those in which the treatment group assignments of study subjects are not known) and unblinded interim analyses. Although advanced planning is preferred, it is still acceptable to make study modifications that have not been prospectively planned as long as the personnel involved have remained blinded. In contrast, unblinded analyses must be planned before a trial begins or they raise major concerns about the potential for bias (FDA, 2010c).

In general, adaptive designs are not intended to be solutions for inadequate planning (Gallo *et al.*, 2006). They can be useful for pediatric studies that may be difficult to plan due to inadequate information. For example, to calculate an appropriate sample size, information is needed from previous comparable studies (i.e., those that included similar populations of children to the current investigation), but this information may be unavailable (Van der Tweel *et al.*, 2012). Using an adaptive design, sample size can be increased after interim analysis to maintain study power or the study can be lengthened to obtain additional endpoint events (FDA, 2010c).

Sequential designs are more established than adaptive designs and have been used in several pediatric trials. In a systematic review of trials involving children (aged 0 to 18 years) up to July 2007, Van der Lee *et al.* (2010) identified 24 RCTs that employed sequential designs. Thirteen of these were performed in a neonatal intensive care setting. For example, Lin *et al.* (1999) investigated the efficacy of early dexamethasone therapy in preventing chronic lung disease (CLD) in pre-term newborns. The study was discontinued when statistical significance favouring dexamethasone was reached by sequential analysis. To reach significance, 12 pairs in which one infant had CLD and the other did not were required (Lin *et al.*, 1999). Published examples of pediatric trials using adaptive designs are virtually non-existent, except for a controversial example examining the efficacy of extracorporeal membrane oxygenation (ECMO) in newborns with respiratory failure compared to conventional ventilator therapy (Bartlett *et al.*, 1985). This study used responsive adaptive randomization, a design in which the probability of being allocated to the more successful treatment group continually increases as efficacy data accumulates (Friedman *et al.*, 2010).

In their guidance document on adaptive design clinical trials, the FDA (2010c) identifies two principal issues with adaptive designs. The adaptation process may (i) lead to “design, analysis or conduct flaws that have introduced bias that increases the chance of a false conclusion that the treatment is effective (a Type I error);” and (ii) generate “positive study results that are difficult to interpret.” A longer and more onerous planning phase will likely be required owing to the complexity of adaptive designs and the trial itself may take longer to complete if more events are needed (FDA, 2010c). In addition, interim results may oscillate early in a trial, and adapting its design according to these emerging or non-emerging trends may constitute an overreaction and lead to inappropriate decision-making in trial management (Friedman *et al.*, 2010).

Despite these potential problems, adaptive designs can be useful and methodologically sound if organizational and statistical issues are considered carefully (Mehta *et al.*, 2009; Mehta & Pocock, 2011). Although methodologists have demonstrated increasing enthusiasm for these designs, investigators and sponsors have thus far been reluctant to undertake them in practice (Mehta & Pocock, 2011). The FDA encourages researchers to gain more experience with these designs during the earlier exploratory phase of drug development, in which initial studies may be undertaken to guide future decisions on the best methods for studying a drug (FDA, 2010c). Even at later stages, adaptive designs may be useful when there are constraints on time, resources, and available patients for a trial, since they can provide the same information as a conventional study with more efficiency (FDA, 2010c; Baiardi *et al.*, 2011).

5.5.2 Using an Active Comparator

Trial designs with various types of controls can each provide evidence of efficacy. Studies with active comparators may seek to show that the investigational drug is more effective than the comparator (a *superiority* trial) or not inferior to the comparator (a *non-inferiority* trial). For the latter, an explicit external criterion — referred to as the *margin* — for a clinically relevant difference is needed (e.g., an improvement equal to or less than 10% in the primary outcome is considered non-inferiority while an improvement greater than 10% is considered superiority). Thus, while the new treatment may not be equivalent to the active comparator, the aim of a non-inferiority trial is to show that the difference between the two treatments is small enough to consider the new drug to be within the same (clinical) efficacy range as the comparator (FDA, 2010a). In other words, the goal is to demonstrate that the experimental treatment is “not unacceptably worse” than the active comparator (Fleming & Powers, 2008). The choice of comparator should be based on the state of the evidence. The FDA and EMA have published guidance documents

to help with issues such as choosing an appropriate non-inferiority margin and interpreting the results of superiority and non-inferiority trials (EMA, 2000, 2005; FDA, 2010a).

When an established, effective therapy exists, randomizing patients to a placebo control may be viewed as unethical. Thus, reduced acceptability concerns of active comparator trials make larger sample sizes easier to recruit, which is particularly beneficial for rare disease trials in children (Abrahamyan *et al.*, 2014). In addition, unlike placebo-controlled trials, which can only demonstrate whether a new treatment is better than no treatment, active comparator trials can determine relative efficacy (i.e., whether one treatment is more effective than another). Physicians may view this information as more valuable since it can help with prescribing decisions (Halpern *et al.*, 2002).

When interpreting data from active comparator trials, the following points must be considered. First, these trials rely on existing evidence that the active comparator has been shown to be effective; without this evidence, demonstration of efficacy in a non-inferiority trial is not possible (ICH, 2000b). However, a superiority trial may be possible without evidence of efficacy of the active comparator if the typical standard of care has not been proven effective. For example, in certain situations, a placebo control may be considered unethical, but there may not be any available treatments that have unequivocally demonstrated efficacy in placebo-controlled trials (e.g., for some types of cancer or rare diseases). In these cases, the investigational drug could be compared to the available standard of care in a superiority trial (EMA, 2005).

Second, choosing an active comparator can be challenging. To reliably assess the efficacy of the new drug, the performance of the comparator in the setting of the current trial should be similar to its performance in previous trials (often called the *constancy assumption*) (Fleming, 2008). Third, it may be difficult to ascertain a credible, clinically meaningful non-inferiority margin that should be met in the study (FDA, 2010a). Finally, because non-inferiority trials may lead to approval of a therapy even if it is less effective than its comparator, after several generations of non-inferiority trials, in which each new drug is slightly worse than its predecessor, an ineffective therapy may be falsely deemed effective (Fleming, 2008; Everson-Stewart & Emerson, 2010).

5.5.3 Addressing Perceived Acceptability Concerns by Using Alternatives to Parallel Group RCTs

Numerous modifications can be made to RCTs to address perceived acceptability concerns. If no established treatment is available, but parents and physicians are still reluctant to enroll children in a placebo-controlled trial, study designs that decrease the amount of time spent on placebo or ensure that all patients eventually receive the treatment may be considered. In certain circumstances, such as time-sensitive life-or-death situations, it may be difficult to obtain prior informed consent. Although there are established methods for temporarily delaying the obligation to obtain consent, this may not be possible in all cases. In addition, RCTs may not be feasible or even necessary for examining certain interventions involving children with diseases that have extremely high mortality rates; rather, observational studies combined with the use of historical controls may be more appropriate. Situations in which the effects of treatment are dramatic (e.g., immediate/rapid or beneficial in a high proportion of patients) and easy to separate from the natural (untreated) outcome may not require RCTs (Glasziou *et al.*, 2007).

One example of such a situation is severe perinatal or infantile hypophosphatasia, a condition that leads to defective bone mineralization and possible death from respiratory compromise. An approved medical treatment does not exist. In a study published in 2012, all enrolled patients had life-threatening or debilitating hypophosphatasia and all were treated with an enzyme replacement therapy, resulting in dramatic improvements in all patients who completed at least one year of therapy (Whyte *et al.*, 2012). Table 5.1 reviews several modifications or alternatives to RCTs that can address acceptability concerns.

Table 5.1
Alternatives to Parallel Group RCTs that Address Perceived Acceptability Concerns

Design Characteristics	Advantages/Disadvantages	Example of Published Study Using Design	Context in Which Design May be Used
Randomized Placebo-Phase Design (RPPD)			
<ul style="list-style-type: none"> • Patients started on placebo and randomized to begin treatment at various times. • If treatment is effective, patients who receive it sooner have a higher probability of responding sooner. 	<p>Advantages</p> <ul style="list-style-type: none"> • All patients eventually receive treatment. • Subjects and researchers blinded as to when switch occurs. <p>Disadvantages</p> <ul style="list-style-type: none"> • Limited to potent therapies with rapid effects (treatment effects likely impossible to capture for therapies with longer and highly variable response times). • Less statistical power than classic RCTs and thus may require larger total sample sizes. • Placebo and active treatment cannot be directly compared. 	<ul style="list-style-type: none"> • Examined efficacy of rituximab, a biologic for treatment of refractory adult and juvenile myositis. • No significant difference in clinical response time between early and late treatment arms. • Treatment effect not rapid enough to measure difference. (Oddis <i>et al.</i>, 2013) 	<ul style="list-style-type: none"> • Studies of curative or symptomatic treatments for which a long-term control arm is thought to be infeasible or unacceptable.
Cross-Over Design			
<ul style="list-style-type: none"> • Each patient receives two or more treatments in a random order (e.g., placebo and treatment groups switch for second half of study). 	<p>Advantages</p> <ul style="list-style-type: none"> • Compares multiple treatments in the same patient, which produces less variable results than between-patient comparisons, thus allowing use of smaller sample sizes. <p>Disadvantages</p> <ul style="list-style-type: none"> • Inappropriate for treatments with prolonged, permanent, or curative effects. • Disease/condition must be chronic and stable. • Limited to drugs with short half-lives that will not lead to carry-over effects. 	<ul style="list-style-type: none"> • Examined effect of intranasal gentamicin on patients with cystic fibrosis (a chronic genetic disease). • Treatment was effective in patients with a certain type of mutation. • Design chosen due to variable presentation of disease (conductive to within-patient comparison). (Wilschanski <i>et al.</i>, 2003) 	<ul style="list-style-type: none"> • Reversible therapies. • Drugs with relatively rapid onset of action and washout. • Common design in pediatric research.

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Design Characteristics	Advantages/Disadvantages	Example of Published Study Using Design	Context in Which Design May be Used
Enrichment Design: Randomized Withdrawal			
<ul style="list-style-type: none"> Product is tested in an enriched population. All patients are treated to identify responders; trial is continued only with responders, who are randomized to treatment or control. 	<p>Advantages</p> <ul style="list-style-type: none"> Power of comparison increased by using responders only, so easier to achieve significance with small sample sizes. Reduced amount of time spent on placebo. Patients on placebo can begin receiving treatment again once their symptoms have reappeared. <p>Disadvantages</p> <ul style="list-style-type: none"> Treatment will be withdrawn from children who are benefitting from it if they are randomized to placebo group. Limited to drugs with short half-lives that will not lead to carry-over effects. No direct comparison of response to placebo/control. 	<ul style="list-style-type: none"> Investigated efficacy of an immunotherapy for juvenile idiopathic arthritis. Therapy significantly decreased the risk of symptom reappearance. All patients (including non-responders) were offered therapy for a further 5 years and treatment was effective even in some non-responders. (Ruperto <i>et al.</i>, 2008; Ruperto <i>et al.</i>, 2010) 	<ul style="list-style-type: none"> Reversible therapies. When a parallel group placebo-controlled study is thought to be inappropriate. Design has been used extensively in pediatric rheumatology trials.
Prospective Observational Study			
<ul style="list-style-type: none"> An outcome (e.g., survival), a population of interest (e.g., pre-term infants), and at least two interventions (e.g., treated and untreated) are chosen prospectively. Patients are enrolled based on pre-determined eligibility criteria but are treated on an individual basis instead of being randomly assigned to an intervention. May use propensity score* matching. 	<p>Advantages</p> <ul style="list-style-type: none"> Patients are treated on a case-by-case basis, which may be the only option when random assignment is not acceptable. Parents more likely to consent (child will get individual care). A more practical design for urgent therapeutic interventions in which the short timeframe and stress level of parents may make enrollment in an RCT difficult. <p>Disadvantages</p> <ul style="list-style-type: none"> Prono to confounding (especially confounding by indication), which occurs when an exposure appears to be affecting an outcome, when, in reality, another factor associated with the exposure is actually causing the outcome. 	<ul style="list-style-type: none"> Compared in-hospital morbidity and survival of extremely pre-term infants who received or did not receive anti-hypotensive therapy. A previous study showed that an RCT approach was not feasible (a major issue was lack of parental consent). Certain morbidities were more common in treated infants, but overall regression analysis indicated no survival or morbidity difference between groups. (Batton <i>et al.</i>, 2012; Batton <i>et al.</i>, 2013) 	<ul style="list-style-type: none"> For rare exposures (small sample size of eligible subjects). When RCTs are thought to be infeasible. Most often used to study safety (not efficacy).

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Design Characteristics	Advantages/Disadvantages	Example of Published Study Using Design	Context in Which Design May be Used
Retrospective Observational Study			
<ul style="list-style-type: none"> • Similar to above, an outcome, population, and at least two interventions are chosen. • Data collected retrospectively, from patient charts, registries, databases, etc. • May use propensity score matching. 	<p>Advantages</p> <ul style="list-style-type: none"> • None of the ethical issues surrounding experimental studies apply, since data are collected after the fact. • Informed consent not required. <p>Disadvantages</p> <ul style="list-style-type: none"> • Data may be difficult to compare between groups due to missing information in charts, databases, etc. and variable methods. • Risk of bias and confounding if mathematical methods such as propensity score matching are not used to equalize groups. 	<ul style="list-style-type: none"> • Examined impact of an antiviral on length of hospital stay for critically ill children with influenza. • Treated and untreated patients were matched by propensity score. • Data taken from Pediatric Health Information System (PHIS) database. • Treatment was associated with a shorter hospital stay. (Coffin <i>et al.</i>, 2011) 	<ul style="list-style-type: none"> • For rare exposures (small sample size of eligible subjects). • When RCTs are thought to be infeasible. • Most often used to study safety (not efficacy).

Data Source: Campbell *et al.* (1998); ICH (2000b); Feldman *et al.* (2001); Elbourne *et al.* (2002); Jepsen *et al.* (2004); Reed (2004); Strom (2005b); WHO (2007); Baiardi *et al.* (2011); Batton *et al.* (2012); IOM (2012a); Abrahamyan *et al.* (2014)

* Propensity score matching is a bias correction method that enhances comparability between groups. A propensity score is assigned to each individual, which is created using his or her baseline characteristics. Groups can then be classified using this score, and data can be adjusted accordingly. With propensity score methods, retrospective studies can be completed using observational data (e.g., patient charts), and confounding can be reduced after the fact to provide an unbiased estimate of treatment effect. These methods can also be used for prospective observational studies to deal with study groups that are non-comparable due to lack of random assignment. An important point is that any correction methods can only be applied to confounding variables that are known and measured, and some types of confounding are more likely to be measured than others (Johnson *et al.*, 2012; Abrahamyan *et al.*, 2014).

Designs based on modified RCTs may be particularly appealing for studies in children for multiple reasons. First, they allow all participants to experience a new, potentially beneficial treatment. This may enhance acceptability for investigators, parents, and children, resulting in higher study enrollment (Baiardi *et al.*, 2011; Abrahamyan *et al.*, 2014). Second, some of these designs can recruit smaller samples, since they increase the power of comparison (enrichment design) or compare multiple treatments within the same patient (cross-over design), allowing statistical significance to be achieved with fewer participants. While they do possess some limitations (e.g., several can be used only with *reversible* therapies with short-lived, non-curative effects), modified RCTs may allow certain studies to be completed when a classic parallel group RCT is not feasible.

In certain rare and extreme cases (e.g., when it is difficult to obtain parental consent), observational studies may need to replace RCTs. Observational studies may be particularly important for rare pediatric diseases; patients with these diseases are often followed at specialized centres where they can be observed collectively (Abrahamyan *et al.*, 2014). However, a major disadvantage of observational study designs is their inability to control for unknown or unobserved potential biases. In addition, their validity relies on previous evidence that the effect seen in observational studies is sufficiently robust to circumvent the need for a concurrent control. Observational studies are more applicable to post-marketing safety studies that aim to quantify the risks of adverse reactions, as discussed in Chapter 6. Nonetheless, a central requirement when studying pediatric drugs is the willingness to consider the use of alternative approaches when parallel group RCTs are unacceptable or infeasible. As mentioned, investigators should consult regulatory agencies before using alternative designs for drug efficacy studies if these studies are being performed for the purpose of regulatory approval.

5.5.4 Handling Small Target Populations

Lower incidence of certain conditions among children as compared to adults, such as cancer (Unguru, 2011) or kidney disease (Foster & Warady, 2009), and low enrollment in pediatric clinical trials for reasons such as parental anxiety, make it challenging to recruit enough children to adequately power an RCT. Because of low disease incidence, exceedingly small numbers of eligible patient-participants may be receiving care at a single institution. Multi-centre studies are one potential solution to this challenge, since they allow geographically dispersed individuals to be included in a single study. Multi-centre approaches used by collaborative research group, such as the Children's Oncology Group (COG) (see Box 5.2), represent a powerful method for performing efficacy studies in children.

In some cases, the small number of eligible patient-participants may preclude single-centre RCTs but the resource networks for a multi-centre study may not be in place. Multiple n-of-1 trials attempt to address this methodological challenge by measuring the efficacy of a therapy compared to a placebo for an individual patient (a sample of one), with the patient serving as his or her own control. In multiple successive periods, placebo or treatment is administered in a double-blind, randomized manner, and patient response is measured after each period (Johannessen, 1991). The n-of-1 methodology became more prominent in the medical literature in the mid-1980s, and Canadian researchers have been leaders in its development (Gabler *et al.*, 2011). For example, in 1988 Guyatt *et al.* (1990) initiated a service to assist clinicians in conducting n-of-1 trials and subsequently published detailed guidelines for clinicians to conduct their own trials. The service-based approach was used by Nikles *et al.* (2006) to help clinicians determine optimal medication regimens for children with attention deficit hyperactivity disorder (ADHD). The advantages and disadvantages of multi-centre studies and n-of-1 trials are discussed in Table 5.2.

Box 5.2

Spotlight on Multi-Centre Studies Performed by the Children's Oncology Group (COG)

Pediatric oncology is viewed as one of the best examples of integrating patient care with medical research (Unguru, 2011). Approximately 70% of children with cancer participate in a clinical trial during their illness (Joffe *et al.*, 2006). Early success in the treatment of childhood leukemia led to the development of principles and guidelines that could be applied to other childhood cancers. Achievements in this area resulted from the realization that large cooperative groups would be necessary to study pediatric cancer, given its rarity. The first of these was the Cancer Chemotherapy National Committee, formed in the United States in 1954 by researcher Sidney Farber. One year after its formation, nearly 40 hospitals were already participating in multi-centre cancer trials. Several other groups were subsequently established, culminating in the formation of the current cooperative, the Children's Oncology Group (COG). COG includes members from 240 pediatric cancer centres in seven countries, including Canada (Unguru, 2011).

As the classification of major types of childhood cancer has increased in complexity, it has become even more difficult to obtain large enough sample sizes for a given disease, which has intensified international collaboration. At each COG centre, patients are treated using standard COG protocols (O'Leary *et al.*, 2008). This presents a major advantage not only within a single multi-centre study but also between studies. For example, Schultz *et al.* (2009) used a historical control — a group of patients who were treated at an earlier time. Though comparing groups treated at different times in different studies may be considered risky, the standardization of protocols within COG trials makes an indirect comparison valid and rational. These studies are often complex, involving several treatment arms with different doses, schedules, and therapies, making it practical to avoid including an additional treatment that has already been tested in a previous COG study.

The power of collaboration is ultimately demonstrated by publications that review decades of multi-centre trials. For example, a 2010 COG study compared results from 13,298 acute lymphoblastic leukemia patients treated with 16 different protocols (Gaynon *et al.*, 2010), which led to several critical observations on treatment success and trial design.

Table 5.2
Methods for Handling Small Target Populations

Description of Method	Advantages/Disadvantages	Example of Published Study Using Design	Context in Which Design May be Used
<p>Multi-Centre Studies</p> <ul style="list-style-type: none"> Involve the collaboration of several sites. Often rely on international research networks and registries (e.g., the North American Pediatric Renal Trials and Collaborative Studies registry). 	<p>Advantages</p> <ul style="list-style-type: none"> Ideal for rare diseases in which few patients are available at each centre. Results may be more generalizable since participants represent a wider geographical area. <p>Disadvantages</p> <ul style="list-style-type: none"> Inconsistencies in study protocols, execution of procedures, and measurement of outcomes may occur between study centres. Each participating site must obtain approval from their Research Ethics Board (REB). 	<ul style="list-style-type: none"> Evaluated efficacy of intensive chemotherapy plus imatinib in children with high-risk acute lymphoblastic leukemia. Children treated at multiple centres by Children’s Oncology Group affiliated researchers. Compared with historical controls treated with chemotherapy alone, imatinib in combination with chemotherapy improved event-free survival. <p>(Schultz et al., 2009)</p>	<ul style="list-style-type: none"> All therapeutic trials.
<p>Multiple N-of-1 Trials</p> <ul style="list-style-type: none"> In multiple successive periods, placebo or treatment is administered in a double-blind, randomized manner. Patient serves as his or her own control. 	<p>Advantages</p> <ul style="list-style-type: none"> A series of n-of-1 trials can be used to estimate treatment efficacy for a population by employing Bayesian statistical modelling. Allow for an efficient use of resources and patients when large-scale parallel group studies are not possible. Number of treatment/placebo periods and total duration of study can be different in each subject. Help to develop tailored therapeutic regimens that work in individual patients. <p>Disadvantages</p> <ul style="list-style-type: none"> Similar to cross-over designs (Table 5.1); treatment effects cannot be prolonged or curative. Condition must be sufficiently stable and long-lasting to allow for repeated periods of treatment and placebo. Fast-acting drug preferred (can allow for shorter treatment periods). 	<ul style="list-style-type: none"> Used a series of n-of-1 trials and Bayesian analysis* to estimate comparative efficacy of a single anti-nausea and -vomiting drug versus a combination of two drugs in children with brain tumours receiving highly nausea-causing chemotherapy. Data from 10 patients suggested that combination therapy was superior to monotherapy. <p>(Nathan et al., 2006)</p>	<ul style="list-style-type: none"> Reversible therapies. Drugs with relatively rapid onset of action and washout. Situations in which disease rarity precludes parallel group RCTs. <p>* See Section 5.6.1 for a discussion of Bayesian analysis.</p>

Data Source: Johanssen (1991); Greene and Geiger (2006); Foster and Warady (2009); Unguru (2011); Abrahamyan et al. (2014)

Multi-centre studies are highly effective when dealing with inadequate numbers for enrollment and, in cases of rare childhood diseases, may be the only way to perform large enough parallel group RCTs to obtain useful information. If various elements are in place, such as a well-developed study infrastructure and a clinical coordinating centre that regularly interacts with investigators and support staff at different sites, a multi-centre study may be the best solution for handling small sample sizes (Foster & Warady, 2009). Although parallel group RCTs are considered to produce the highest level of evidence when assessing the effect of a therapeutic intervention (Baiardi *et al.*, 2011), methods such as multiple n-of-1 trials should not be dismissed. Regulatory agencies such as the EMA recognize that n-of-1 trials may be a legitimate alternative when parallel group RCTs are not possible (EMA, 2006b). For some rare childhood diseases, established research networks such as COG (Box 5.2) may not exist, and multiple n-of-1 trials provide an additional avenue for including children in research. However, as with other alternative designs, investigators should discuss their use with regulatory agencies since n-of-1 trials are not yet viewed as standard practice.

5.6 ANALYSIS TECHNIQUES THAT SUPPORT PEDIATRIC STUDIES

Section 5.5 focuses on modifications to trial design that can enhance their flexibility, acceptability, and feasibility, thereby encouraging the completion of efficacy studies in children. In addition to alternative designs, various analytical approaches can help with planning trials and analyzing trial data. These approaches may be useful for supporting classic parallel group RCTs or modified designs.

5.6.1 Bayesian Analysis

The traditional method for analyzing data in the medical field is known as *frequentist statistics*, which relies on an index to measure the strength of evidence called the *p-value*. The p-value is defined as the probability of obtaining a result equal to or more extreme than the observed result, under the assumption of no difference (i.e., by chance alone). Using this mathematical approach, background information and biological understanding are considered less formally, along with the results of significance tests, in the interpretation of clinical results (Goodman, 1999b). Bayesian and frequentist approaches are both informative and can be used in complementary ways to analyze treatment effects.

In contrast to frequentist methods, Bayesian methods allow evidence from different experiments to be combined intuitively (Goodman, 1999a). A Bayesian analysis integrates data from prior studies with those of the current study to yield a new probability distribution from which to draw conclusions (Abrahamyan *et al.*, 2014). Because this approach takes advantage of all of the available information for a given experimental therapy, the study that is currently being undertaken may be able to use fewer subjects. This situation is ideal for children because it is often difficult to recruit enough participants for a trial. In addition, prior information from adults may sometimes be used in the analysis of pediatric data (Schoenfeld *et al.*, 2009; Baiardi *et al.*, 2011). For example, Goodman and Sladky (2005) performed a study to explore how Bayesian methods could be used to determine the relative efficacy of two treatments (plasmapheresis and intravenous immune globulin) for a disease that occurs extremely rarely in children (Guillain-Barré Syndrome). The authors used prior data on treatment efficacy from adults to construct a probability curve that could be applied to a small set of pediatric data (Goodman & Sladky, 2005). In addition, as opposed to frequentist analysis, Bayesian analysis yields a direct probability statement about the treatment under study. In this way, Bayesian methods are also particularly helpful for rare diseases, since they can be used to reanalyze small RCTs, potentially providing useful information from studies that were previously inconclusive when considered from a frequentist viewpoint (Abrahamyan *et al.*, 2014).

Bayesian analyses are perhaps most helpful in situations in which applicable prior information is available. However, Abrahamyan *et al.* (2014) discuss the fact that including prior information is controversial. Some may doubt whether the prior information is correct. In addition, the way in which prior information is used is subjective (but, at least, explicit) (Spiegelhalter *et al.*, 2000). However, there are methods to deal with these uncertainties. Researchers can choose to use *non-informative priors* (in which no assumptions are made about prior data) or can use a *family of priors* (e.g., optimistic and sceptical priors) that should satisfy all users of the research.

The Bayesian approach can also be used in an adaptive design (see Section 5.5.1) to modify a trial based on updated predictive probabilities. Although this approach is complex, computational advances have made it more feasible (Howard *et al.*, 2005). Despite these controversies, Bayesian methods may be particularly useful for supporting pediatric efficacy trials, particularly when data are limited by small sample sizes.

5.6.2 Extrapolation

In 1994, the FDA finalized a set of conditions that must be met to permit extrapolation of drug efficacy data from adults to children or from pediatric patients in one age group to another (Dunne *et al.*, 2011). The *Pediatric Research Equity Act* (PREA) permits extrapolation of efficacy but not safety or dosing. Due to developmental differences between adults and children, pediatric pharmacokinetics and safety are generally difficult to predict based on adult information and should therefore be studied by conducting drug trials in children (FDA, 2013d). Full extrapolation, which is explained below, assumes that a drug with proven efficacy in adults will also be effective in children (for the same indication) if the following parameters are similar in the two populations:

- The course of the disease;
- The exposure–response relationship (i.e., when the drug reaches a blood concentration in children that is equivalent to that in adults, it will produce a similar response);
- The outcome following therapy (i.e., the overall effect of the drug and thus the response to drug treatment are similar).

(ICH, 2000a; Bellanti & Della Pasqua, 2011; Dunne *et al.*, 2011; FDA, 2013d)

The FDA approach is generally supported by the ICH and the EMA; however, the EMA has emphasized more explicitly development and testing of hypotheses on age-related clinical pharmacological differences and has called for the development of a more comprehensive set of approaches and methodological rules (ICH, 2000a; EMA, 2012b). The FDA developed a pediatric study decision tree to guide researchers through the process of determining whether extrapolation can contribute to pediatric approval of a given drug. If none of the above assumptions apply, then a full study program may be necessary, including pharmacokinetic studies to establish dose, as well as safety and efficacy trials. If all of the requirements are met, then only pharmacokinetic studies (to achieve drug levels similar to adults) and safety studies are required, which is considered *full* extrapolation. If all but the exposure–response relationship apply, then pharmacokinetic and pharmacodynamic studies are needed to link exposure levels with outcome measurements (such as biomarkers of clinical endpoints) that support *partial* extrapolation of efficacy (EMA, 2012b; Nelson, 2013). As mentioned in Section 3.5.1, modelling and simulation (M&S) may help to support some of these options (e.g., by selecting a range of doses to study) (Manolis *et al.*, 2011; FDA, 2014b).

Advantages and Limitations of Extrapolation

Due to issues already discussed in this chapter — such as parental hesitancy and low numbers of potential pediatric study candidates — fewer children are available to enroll in clinical trials. Thus, in reducing the number and complexity of clinical trials that are necessary for pediatric drug approval, extrapolation can make the drug development process less burdensome for children as well as faster and more efficient (Dunne *et al.*, 2011; FDA, 2014b).

In a review of pediatric studies submitted to the FDA between 1998 and 2008 in response to written requests, Dunne *et al.* (2011) found that extrapolation was used frequently and drugs were more likely to receive a new pediatric indication or extension to a new age group when extrapolation was employed. However, this result was at least partially attributed to the fact that diseases for which extrapolation is not feasible are generally not as well-researched, possibly because they are pediatric-specific; thus, efficacy trials may suffer from this lack of knowledge (e.g., appropriate endpoints) and may be more likely to fail (Dunne *et al.*, 2011). For example, pediatric cancer is not amenable to extrapolation since pediatric tumours are biologically distinct from adult tumours (FDA, 2014b).

A qualification of this study by Dunne *et al.* (2011) is that complete extrapolation (cases in which only pharmacokinetic and safety studies — or, in rare cases, only safety studies — were conducted with children) was used for less than 15% of the products. Furthermore, it primarily supported the extension of indications or age groups or the approval of new formulations for drugs that were previously approved in children, rather than extrapolation from adults to children. Partial extrapolation, which still involved at least one pediatric efficacy trial, was much more common. As stated by Dunne *et al.* (2011), “[t]here is no simple formula to determine whether there is adequate evidence to support the decision to extrapolate efficacy to the pediatric population.” The method is still evolving as knowledge accumulates.

5.7 CHALLENGES IN CARRYING OUT EFFICACY STUDIES IN CHILDREN

In addition to the methodological challenges involved in researching the efficacy of pediatric therapy, challenges that relate to ethics and standardization also deserve careful consideration. Most of these concerns apply to a wide range of different study types rather than particular study designs. For these reasons, this report discusses these challenges in general terms.

5.7.1 Key Initiatives Working to Address the Challenges of Pediatric Research

There is international consensus on the importance of improving the quantity, quality, and accessibility of pediatric trial data. Several initiatives (Table 5.3) have developed guidelines, standards, and databases to facilitate ethical and consistent acquisition of data as well as logical reporting and storage of information. In addition to improving standardization, the European Union and its member states have recognized the need for support networks to deal with the logistical issues of clinical trials. See Box 5.3 for a discussion of the Medicines for Children Research Network in the United Kingdom.

Table 5.3

Key Pediatric Research Initiatives

Standards for Research in (StaR) Child Health (StaR Child Health, 2012)			
Date established 2009	Mandate "To improve the design, conduct, and reporting of pediatric research through the development and dissemination of evidence-based standards" (Hartling <i>et al.</i> , 2012b).	Examples of affiliated organizations • GRiP	Activities • Developing a set of uniform standards for pediatric trials that address challenging areas in pediatric research, including ethics and statistical validity.
Global Research in Paediatrics (GRiP) (GRiP, 2014)			
Funding period 2011–2015	Mandate To "facilitate the development, and promote the availability, of medicines for children" (GRiP, 2013).	Examples of affiliated organizations • SickKids • NICHD • EMA • WHO	Activities • Working to reduce the fragmentation of current research efforts in pediatrics and develop harmonized standards, methodologies, and tools for researchers in areas, such as clinical trials, post-marketing studies, and newborn drug development. • Developing an internationally recognized pediatric clinical pharmacology training program.
National Institute of Child Health and Human Development (NICHD) (NICHD, 2014)			
Date established 1962	Mandate To study the "complex process of human development from conception to old age" (NICHD, 2012).	Examples of affiliated organizations • NICHD is an official institute of the NIH	Activities • Conducts research; funds grants, awards and training programs; and provides guidance for researchers. • Began the Pediatric Terminology Harmonization Initiative in 2009 to establish a library of terms for facilitating comparison and combination of data collected by different investigators (NICHD, 2011).

continued on next page

World Health Organization – Better Medicines for Children Programme (WHO, 2014b)				
Date established 2007	Mandate To address numerous global deficiencies in the development, formulation, regulation, and distribution of medicines for children (WHA, 2007).	Examples of affiliated organizations <ul style="list-style-type: none"> • Health Canada • EMA • FDA • Swissmedic 	Activities <ul style="list-style-type: none"> • Contributes to the standardization and harmonization of pediatric trials by publishing guidance documents such as WHO (2011). • Maintains a Clinical Trials in Children portal within the WHO International Clinical Trial Registry Platform and a Pediatric medicines Regulators' Network (PmRN) (WHO, 2014a). 	
European Network for Paediatric Research at the EMA (Enpr-EMA) (EMA, 2012e)				
Date established 2009	Mandate <ul style="list-style-type: none"> • To build and strengthen scientific, technical, and administrative competence related to pediatric clinical trials through effective collaboration. • Reduce duplication of effort, improve efficient use of infrastructure, and develop common methodologies. 	Affiliated members include those with: <ul style="list-style-type: none"> • Research experience and ability; • Network organization and processes; • Scientific competencies; • Quality management; • Training and educational capacity; and • Public involvement. 	Examples of affiliated networks <ul style="list-style-type: none"> • MICYRN • MCRN • PRINTO • PENTA 	Activities <ul style="list-style-type: none"> • Act as a platform for communication with industry and patient organizations. • Develop common models and educational tools to increase trial awareness and enrollment and improve trial planning and implementation. • Develop specialty networks to stimulate the development of new European-wide clinical trial networks. • Showcase model Paediatric Investigation Plans (PIP).

Abbreviations: EMA (European Medicines Agency); FDA (U.S. Food and Drug Administration); MICYRN (Maternal Infant Child and Youth Research Network); MCRN (Medicines for Children Research Network); NIH (U.S. National Institutes of Health); PRINTO (Pediatric Rheumatology International Trials Organisation); PENTA (Paediatric European Network for Treatment of AIDS); SickKids (Hospital for Sick Children–Toronto); Swissmedic (Swiss Agency for Therapeutic Products).

Box 5.3

Support of Child Health RCTs in the United Kingdom: The MCRN

The numerous logistical aspects that must be considered when planning and implementing pediatric clinical trials may seem overwhelming for researchers. In 2005, the United Kingdom established the Medicines for Children Research Network (MCRN) to “improve the co-ordination, speed and quality of randomized controlled trials and other well designed studies of medicines for children and adolescents” (MCRN, 2011a). Although the network does not provide funding, it offers a comprehensive infrastructure to facilitate studies sponsored by public funding bodies or the pharmaceutical industry. MCRN was developed, in part, to deal with the anticipated increase in demand for commercially sponsored pediatric trials following implementation of the *Paediatric Regulation* in the European Union (Nunn, 2009).

Through the MCRN Coordinating Centre, Clinical Studies Groups (devoted to different areas of child health such as metabolic disorders, neurosciences, and rheumatology), and Local Research Networks, researchers from academia and industry can obtain assistance with refining research questions, setting up collaborations, designing studies, performing feasibility assessments (to determine whether a study is likely to be successful), setting up study sites (including obtaining ethics approval), recruiting patients, managing research staff, and addressing regulatory requirements upon study closure (MCRN, 2011b). MCRN works to manage the performance of studies at all stages to ensure that they begin, recruit, and reach completion in a timely manner (Nunn, 2009). Their overall goal is to provide a supportive research culture and reduce the burden for investigators to encourage them to lead and participate in pediatric research projects (MCRN, 2009).

5.7.2 Ethical Aspects of Pediatric Trials

In the 1970s, following criticism of several ethically questionable research projects, the United States Congress established a Commission that published *The Belmont Report: Ethical Principles for Protection of Human Subjects of Research*. The report recommended applying three ethical principles to human research subjects: respect for persons, beneficence (concern for welfare), and justice (National Commission, 1979). These same core principles are the basis for the nationally enforced policy on research ethics in Canada — the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, now in its second edition (TCPS2) (Tri-Council, 2010). Unique to children and other individuals who cannot exercise autonomy, however, is the fact that others acting in their stead must act in their best interests.

Additional issues must be considered when these principles are applied to children. While it is not the intention to provide a detailed account of the range of ethical issues that arise in clinical trials with children, this section focuses on specific issues — respecting children’s autonomy or lack thereof, harms and benefits, informed consent, assent/dissent, communication of results, biobanking, genomics, remuneration issues, and recruitment guidelines.

Previous sections of Chapter 5 (5.4.2 and 5.5.3) discuss the concerns that the public (e.g., parents) and clinicians may have about the acceptability of clinical trial research with children. An additional perspective comes from Research Ethics Boards (REBs). In Canada, experimental therapies cannot be administered without approval of research protocols by REBs. Clinicians and REBs may differ in their opinions on the classification of therapies as experimental, innovative, or commonly accepted (Patenaude *et al.*, 2008), and the content of documents such as consent forms developed by REBs at different centres may vary considerably (Dove *et al.*, 2013).

To help harmonize ethical norms for research involving children and adolescents and to provide guidance for researchers and REBs, the Centre of Genomics and Policy (CGP) at McGill University and the Maternal Infant Child and Youth Research Network (MICYRN) produced *Best Practices for Health Research Involving Children and Adolescents* (CGP & MICYRN, 2012). This document provides an overview of international and Canadian ethical norms and represents the culmination of two years of extensive consultations across Canada. The *Best Practices* document was aided by the work of several noted scholars (Joffe *et al.*, 2006; Ross, 2006; Graham *et al.*, 2013), and summarizes well-known issues in pediatric trials as well as several new issues (described below). Readers are encouraged to review CGP & MICYRN (2012) for a more detailed discussion.

Harms and Benefits of Research

Canadian research ethics procedures reflect international conventions on the importance of evaluating potential benefits and the likelihood and magnitude of harm in research (CGP & MICYRN, 2012). Potential harms may be physical (e.g., pain), psychological (e.g., fear), social (e.g., discrimination), or practical (e.g., loss of time at school), and any harm–benefit analysis should consider both the cumulative harms and the child’s perspective.

The TCPS2 states that children and other incompetent persons are permitted to participate in research only if it serves to directly benefit their health, involves minimal risk and/or offers potential benefit to other children (Tri-Council, 2010). Research participation that presents slightly above minimal risk without direct benefit to the participants is sanctioned in some jurisdictions, such as the United States

(CGP & MICYRN, 2012). However, the apparent differences in permissible risk between jurisdictions may, in fact, reflect variations in risk assessment and interpretation by different governing bodies. CGP & MICYRN (2012) assert that the most widely held definition of minimal risk characterizes it as posing no greater risk than that which is encountered either in daily life or during routine medical examinations.

Despite a standardized definition of minimal risk, its precise application in assigning ethical permissibility to research participation of children in different states of health remains a challenge. It is true that routine medical procedures for gravely ill children are rarely necessary for healthy children. As a consequence, ethicists argue that the theoretical basis, and ethical justification, for pegging the minimal risk measure on experiences with routine medical procedures is inherently flawed (CGP & MICYRN, 2012). If the risks are minimal, or if the child stands to benefit from the treatment being studied (e.g., vaccines or preventative treatments), a few international and Canadian norms permit inclusion of healthy minors. In these situations the least vulnerable minors (e.g., older minors) are considered first, if possible. Likewise, the harms and benefits of research with terminally ill children should also be considered carefully because of their highly vulnerable status (CGP & MICYRN, 2012).

Informed Consent to Research

Central to the informed consent tenet in biomedical ethics is that individuals participate in research voluntarily. An understanding of the purpose, harms, and benefits must be presented to potential participants as clearly and comprehensively as possible. For a child who lacks the capacity to fully understand this information, an authorized third party, most often a parent, provides informed consent on behalf of the child (Tri-Council, 2010). In Canada, depending on the provincial jurisdiction, adolescents may be considered legally competent to provide informed consent either when they reach the age of majority or are considered mature (CGP & MICYRN, 2012).

Providing parents, children, and adolescents with enough information so as to respect guidelines, yet not overburden such participants, is a recurring challenge in research (Caldwell *et al.*, 2012). Moreover, researchers and clinicians should take care to avoid creating a therapeutic misconception²², by helping patients and their families differentiate between a treatment with a clear medical benefit and a clinical trial where the therapeutic benefits are unknown (Durand-Zaleski *et al.*, 2008).

22 *Therapeutic misconception* refers to “the notion that unless otherwise informed, research participants will assume (especially, but not exclusively, in therapeutic research) that decisions about their care are being made solely with their benefit in mind” (Appelbaum *et al.*, 1982).

Assent to and Dissent from Research

According to the UN Convention on the Rights of the Child, an international legal agreement to which Canada is a signatory, children have a right to express their views on all issues affecting them (UN, 1989). Assuming that a child is capable of forming an opinion, this should be taken into consideration in proportion to his or her age, degree of maturity, and cognitive and developmental skills. Furthermore, a minor should receive information from researchers according to his or her own capacity to understand. However, this cannot be tied to any particular age. A child's agreement to participate is termed *assent* rather than *consent*. Equally, a child has a right to *dissent* from participation, provided he or she is able to understand the significance of the research in question or his/her role in it (Dove *et al.*, 2013). When a child or adolescent reaches the legal age or is considered mature enough to provide autonomous consent during the research, this should be sought. The COG Bioethics Committee has provided extensive guidance on this issue, which is supported by CGP & MICYRN (2012). COG recommends that “[c]hildren’s involvement in decisions about research is best viewed along a continuum, ranging from no involvement ... to full decisional authority” (Joffe *et al.*, 2006). At intermediate points along this continuum, investigators should be willing to consider any wishes a child expresses, but should clearly explain to the child whether his or her wishes will govern any final decisions (Joffe *et al.*, 2006).

Communication of Results

New, pressing issues are emerging about the communication and return of research results, for example, providing research participants with individual results revealed by a technique called *whole genome sequencing* (WGS). Debates over the circumstances under which both anticipated and unanticipated findings — the latter termed *incidental findings* — should be returned to participants raise questions about researchers’ professional responsibilities. Generally, the child and/or parents should be made aware of individual research results or incidental findings that have clinical significance during childhood. A finding that is clinically significant is one that may prevent disease or dictate treatment decisions during childhood. The complex nature of harm–benefit balances in communicating incidental findings should be made clear. Parents should be assured that they will receive clinically significant information about their children, especially if the findings reveal preventable disease with treatment options available during childhood (CGP & MICYRN, 2012; Dove *et al.*, 2013).

Biobanking and Secondary Use of Samples

Biobanks — “organized collection[s] of human biological material and associated information stored for one or more research purposes” (HumGen International, 2013) — are gradually becoming a centrepiece of clinical research in Canada,

as they provide valuable information for assessing health and disease causation. However, biobanks also raise questions as to the possible uses, access, and privacy of their associated data, particularly in the context of pediatric research. The development of pediatric-specific policies involves resolving such issues as the long-term enrollment (e.g., 25 years) of children in a study; the long-term use of samples collected from children in research; the growing maturity of the child; the capacity of the child to make independent decisions; and the child's assent/consent for the use of biological samples and data after trial completion. International opinions differ on these matters, with some policies suggesting the use of broad consent (as specific to the context of biobanks serving as resources) and others maintaining that such a practice is unethical (CGP & MICYRN, 2012). Broad consent "permits the continued use of samples and data for future, unspecified research projects [subject to ethics review] without requiring repeated consents" (CGP & MICYRN, 2012). The extent of parents' authority to provide broad consent for their child's contribution to the biobank is complicated by the fact that the child may acquire the legal capacity to consent for himself or herself during the study. Researchers must take heed in considering these potential issues in advance, so that ethical problems are avoided. For example, samples from a child should be traceable to the subject (rather than anonymous) to enable contact (where feasible) with the child once he or she is old enough to provide consent (CGP & MICYRN, 2012). Consent forms should clearly describe the access and privacy policies of the study. If feasible, researchers could also enable a process of communication such as newsletters or websites that list all approved projects that have accessed the participant's data and/or samples (Dove *et al.*, 2013).

Precision Medicine

WGS, although currently restricted mainly to the research domain, has the potential to initiate improvements in harm prediction and, ultimately, treatment and care in the clinical setting (see Chapter 3). The gradual adoption of WGS and other forms of precision medicine involving bioinformatic analysis of complex biomarker data inevitably raises a number of ethical issues with respect to the information generated. By performing WGS and bioinformatic analysis on samples from children, an enormous amount of future health information (e.g., carrier status, predictive or presymptomatic genomic information, susceptibility to common disorders, pharmacogenomic information, and information on non-medical traits) may emerge. Thus, parental and health care provider decisions on how this information is handled will have an important impact on a child's future. Generally, clinical guidelines stipulate that genome-based testing in children is recommended only when there are established and effective treatments available during childhood (ESHG, 2009). Otherwise, testing should be delayed until the child reaches an appropriate age to make an informed choice (Knoppers *et al.*, 2014).

Remuneration Issues

Financial incentives for participating in research can be controversial and become more so when children are involved (Grady, 2005). Although reimbursement of expenses (e.g., transportation, meals) and compensation payments to parents (e.g., for lost earnings, time, inconvenience) or children (e.g., appreciation toys, gift certificates) are reasonable, parents should not receive undue incentive payments that encourage them to enter their child into a research study that poses potential harms (Tri-Council, 2010; Caldwell *et al.*, 2012; CGP & MICYRN, 2012). This issue is particularly salient when evaluating pediatric research protocols in developing countries, where a modest transportation and meal allowance can be several times the minimum daily wage (Caldwell *et al.*, 2012).

Compensation and incentive payments both involve giving participants money for their contribution to a study. However, compensation might involve estimating a reasonable hourly wage and time commitment for a study, then calculating a payment based on these values (referred to as a *wage-payment* model), whereas an incentive might increase the hourly wage to a value that will ensure adequate enrollment (Bagley *et al.*, 2007). Although research in this area is limited, a study by Bagley *et al.* (2007) suggests that a wage-payment model might be appropriate for compensating older children and adolescents who generally understand the role and value of money and the meaning of a wage. Furthermore, because younger children do not have the same understanding, compensation in the form of age-appropriate gifts might be more appropriate (Bagley *et al.*, 2007).

Recruitment Guidelines

To prevent discrimination and to ensure applicability of the results when generalized to a more diverse population, clinicians should avoid preselecting families for participation in clinical trials. In some cases, clinicians may try to protect a particular family from inconvenience if they feel that the study would be too burdensome for the child or the family (Caldwell *et al.*, 2012). Empirical evidence shows, however, that parents prefer that this decision be left to them after they have received full information about trial participation from their doctor (Caldwell *et al.*, 2003). Researchers and clinicians should be sensitive to participant recruitment in low-socioeconomic or at-risk settings. In general, the scientific reasons for involving individuals from these settings should be justified, and benefits and risks should be shared equally among potential participating groups. However, the views of parents and children from these groups on research participation have not been fully investigated (Caldwell *et al.*, 2012).

5.7.3 Standardizing Among Trials

A lack of standardization in areas such as the division of age groups and the choice of outcomes to measure in efficacy trials can make it difficult to interpret and compare the results of pediatric trials. Children who are relatively close in age may have very different responses to drugs; therefore, inconsistent use of age groups may lead to variable results in trials investigating the same drug. Outcome sets need to be standardized across trials and also chosen for their relevance to children. For example, a child's ability to participate in physical activities (e.g., sports) may be more informative than a clinical outcome (e.g., performance on a respiratory test). Inability to compare trials asking similar questions has been identified as an issue in pediatric research, since the selected outcomes, their definitions, the methods for measuring them, and the timing of measurement are often inconsistent (Sinha *et al.*, 2012a).

Standardizing Age Ranges

Major organizations such as the ICH acknowledge that dividing children into distinct age categories is “to some extent arbitrary” (ICH, 2000a). Although age can be an appropriate marker for certain biological or psychological phenomena, it may be a poor correlate in other cases (Williams *et al.*, 2012). Age groups should be chosen based on the medication and the disease being investigated as well as any relevant pharmacological information. Thus, while a standardized general classification scheme would be useful as a starting point, it would not be widely applicable (ICH, 2000a).

A review of RCTs published in the journal *Pediatrics* from the first six months of 2011 revealed that only 25% of studies presented age-subgroup analyses (Contopoulos-Ioannidis *et al.*, 2012). For a medicine that performs consistently across age groups, it may not be critical to have this information. However, as an example, if a drug is effective in infants (28 days to 12 months) but not in toddlers (13 months to 2 years), a study that combines both age groups may incorrectly conclude that, on average, the drug is or is not effective, depending on how the age groups are represented in the study population (Williams *et al.*, 2012). Although single trials may not have enough power to detect age-treatment interactions, including consistent age-based information can facilitate future meta-analyses (Contopoulos-Ioannidis *et al.*, 2012).

StaR Child Health has suggested that the age groups proposed by the NICHD, which were developed in consultation with several major organizations, be used as a starting point and adjusted accordingly for a given study. These age groups are similar to those used by the ICH (see Chapter 3) with some additional categories (e.g., infants/toddlers and early/late childhood are separated).

In addition, StaR Child Health has developed a schema for helping researchers determine the level of impact that age group differences are expected to have on a trial and whether age-subgroup analyses are warranted (Williams *et al.*, 2012).

Selecting a Standard Set of Outcome Measures

Clinical trials are designed to determine the benefits and harms of a treatment by measuring the effect of the treatment on various clinical endpoints. These endpoints may be final (definitive clinical results such as prolongation of life for a terminal condition) or intermediate (changes in surrogate markers that suggest control or progression of a disease) (Sinha *et al.*, 2008). For the results of a trial to be useful, the clinical endpoints and the outcome measures chosen to capture them must be relevant to patients, clinicians, and policy-makers (Sinha *et al.*, 2012a; Williamson *et al.*, 2012). Less effective outcome measures are often surrogate markers, such as tumour regression in cancer trials, which may fail to represent improvement in overall survival or quality of life (Holloway & Dick, 2002). It may be even more challenging to choose useful outcome measures for pediatric trials, since endpoints commonly measured in adult trials may be inappropriate for children. For example, patient-reported outcome measures, which rely on subjects to report how they are feeling or functioning, are impossible or unreliable in certain age groups (Sinha *et al.*, 2012a). At the time of this report's publication, a task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) was developing guidelines for the design and use of pediatric patient-reported outcome (PRO) instruments. The task force recommends several good research practices, such as ensuring that the PRO instrument is appropriate for the target age group by assessing and refining it following testing in children (Matza *et al.*, 2013).

Another major concern is inconsistencies across trials. When researchers investigating the treatment for a condition measure different endpoints or measure the same endpoint using different outcome measures, it is impossible to compare results between trials or to perform meta-analyses (Sinha *et al.*, 2012a). A solution to this issue, as well as to selective outcome measure reporting (discussed below), is to set standard endpoints and outcome measures that are always used and reported for trials examining treatment of a certain condition, regardless of any other outcome measures that researchers may choose to include (Williamson *et al.*, 2005). These have been referred to as *core outcome measure sets* (Sinha *et al.*, 2008; Sinha *et al.*, 2012a). Box 5.4 describes the development of a core outcome measure set for studies exploring asthma in children. Another example stems from the field of rheumatology — a leader in the adoption of core outcome measure sets. In the early 1990s, the American College of Rheumatology and an international initiative called OMERACT (originally “Outcome Measures in Rheumatoid Arthritis Clinical Trials” and now broadened

Box 5.4

Development of a Core Outcome Measure Set for Clinical Trials in Childhood Asthma

When choosing outcome measures to use in clinical trials, it can be difficult for researchers to know which ones are most important for a specific condition. Direction for researchers interested in developing core outcome measure sets is minimal. One approach is to consider outcome measures used in previous clinical trials, but this may over-emphasize less relevant outcome measures that are nonetheless routinely used and may exclude others that are important for patients.

Core outcome measure sets need not be extensive, but should include a group of outcome measures that are particularly meaningful for patients, families, and clinicians to measure the success of treatment. Additional considerations need to be taken into account to tailor outcome measure sets to children (Sinha *et al.*, 2012b).

To develop a core outcome measure set for clinical trials in childhood asthma, Sinha *et al.* (2012b) used a two-round Delphi survey to collect the opinions of clinicians, nurses, young people with asthma (aged 13 to 15 years), and parents of children with asthma (endpoints identified by parents of preschool and school-aged children were considered separately). The Delphi technique is “a structured method for reaching consensus, in which participants complete sequential rounds of questionnaires, with the results of each questionnaire informing the composition of the next” (Sinha *et al.*, 2012b). Surveys asked participants which endpoints they generally reviewed during clinical visits when making decisions about changes in treatment regimens. For both preschool and school-aged children, the frequency and severity of exacerbations and symptoms (daytime and nighttime), and overall quality of life ranked among the top five endpoints. Ability to perform normal activities and physical activities such as exercise or sports were within the top 10 outcomes for school-aged children. Clinicians and parents were generally in agreement, although parents placed more importance on the long-term beneficial effects of therapy (Sinha *et al.*, 2012b).

An important finding from this study was the emphasis on health-related quality of life. A previous study by the authors found that RCTs for asthmatic children tend to concentrate on short-term disease activity while infrequently assessing the effect of therapies on quality of life or long-term outcomes (Sinha *et al.*, 2009). By engaging clinicians, patients, and their families, and by focusing on endpoints that are used for decision-making in clinical practice, the authors produced a core outcome measure set relevant to those prescribing or using therapy.

to stand for “Outcome Measures in Rheumatology”) collaborated to produce a core set of outcome measures to be used in all clinical trials for adult rheumatoid arthritis (Felson *et al.*, 1993; Tugwell *et al.*, 2007). These efforts have succeeded in dramatically decreasing the number of different outcome measures used across rheumatology trials (Tugwell *et al.*, 2007). PRINTO, a pediatric-specific organization with a similar mandate, has also established a set of outcome measures (Ruperto *et al.*, 2011). Although not specifically for children, the COMET (Core Outcome Measures in Effectiveness Trials) Initiative was launched in 2010, with the overall aim of developing a publicly available database of core outcome measure sets for various conditions and providing guidance on developing standardized sets of outcome measures (COMET Initiative, 2011). COMET has partnered with a Canadian research initiative called PORTal (Primary Outcomes Reporting in Trials). While COMET focuses on *which* outcome measures should be used, PORTal focuses on *how* they can be measured to ensure validity and reliability (COMET Initiative, 2014).

After setting common endpoints, researchers should measure the endpoints in a uniform manner and report these in the final publication, regardless of the results (Sinha *et al.*, 2012a). Intentionally omitting results for certain outcome measures, known as *outcome reporting bias*, is defined as “the results-based selection for publication of a subset of the original measured outcome variables” (Williamson *et al.*, 2012). Outcome measure reporting bias in RCTs is a significant problem in published academic literature and can affect the conclusions of later systematic reviews (Kirkham *et al.*, 2010).

5.7.4 Questions in Ethics and Study Design

Despite the progress on the aforementioned challenges, many questions related to ethics and study design and analysis still remain. For example:

- When compensating research participants, what amount of money or other reward would lead them to disregard risk? Are there situations where it is ethical to pay parents (i.e., beyond reimbursement) for the participation of their child in research (Caldwell *et al.*, 2012)?
- How do study recruitment guidelines apply to children in low-socioeconomic or at-risk settings? What are the opinions of parents and children who are part of these vulnerable populations on being approached to participate in a study (Caldwell *et al.*, 2012)?
- Should the risks of a study procedure be evaluated from a child’s perspective (e.g., would significant mental stress from medical procedures such as injections, which are safe from a physical standpoint, be considered unacceptable) (CGP & MICYRN, 2012)? Are there any extraordinary circumstances that warrant consideration of a pediatric trial with greater than minimal risk

that includes healthy children who are unlikely to benefit from the intervention in the trial (Bioethics Commission, 2013b)? Is an even higher level of risk acceptable for children with serious or life-threatening conditions?

- What are the conditions under which incidental findings from pediatric research should be communicated to participants? Given the large amount of data that can be expected to arise in pharmacogenomics studies, incidental findings should be communicated if they are scientifically valid (includes analytical and clinical validity), have significant implications for the health of the child, and effective treatment or prevention is available during childhood or adolescence. REB approval should be obtained and the findings confirmed before any communication (RMGA, 2013). A 2013 report by the Presidential Commission for the Study of Bioethical Issues focused on this issue (Bioethics Commission, 2013a).
- When deciding on age ranges for a study, are subtle variations in age necessary for understanding drug safety and efficacy, or will they lead to the inclusion of unnecessary groups and therefore more subjects in clinical trials (Williams *et al.*, 2012)?
- How acceptable are the various alternative study approaches to regulatory agencies such as Health Canada and to other agencies that influence access to medications? For example, since 1994 the FDA has had guidelines in place for extrapolating pediatric efficacy from adult data, and this method has been used along with supportive evidence from pediatric studies to approve several drugs for children (Dunne *et al.*, 2011). However, while other approaches are discussed in guidance documents produced by the EMA and FDA (EMA, 2006b; FDA, 2010c, 2012b), the extent to which these approaches have been used in practice to achieve pediatric drug approval is unclear.

Some of these issues may need to be evaluated by ethics and regulatory committees on a case-by-case basis, whereas others would benefit from well-defined standards and guidelines. Fostering a culture that supports pediatric drug efficacy studies and providing guidance on the use of various design approaches would further expand the evidence base for child health (see Box 5.3 on the MCRN).

5.8 CHAPTER SUMMARY

Classic parallel group RCTs are still the approach preferred by decision-makers and may be possible in many studies of drug efficacy in children, particularly if multi-centre studies are used to enroll sufficient numbers of participants. However, the methods presented in Section 5.5 clearly indicate that parallel group RCTs are not the only way to acquire evidence when assessing drug efficacy. An essential element when designing efficacy studies for pediatric drugs is flexibility. For children, it may be difficult to predict certain design parameters for a trial (e.g., the sample size required to demonstrate a minimally important

difference) if the pediatric population under study has not been previously investigated. Flexibility may be achieved using various modifications such as adaptive or sequential designs. Incorporating the views and perspectives of children, parents, and clinicians is important. Children do not have the capacity to understand the harms and benefits of a clinical trial. Because of children's vulnerability, parents and clinicians may hesitate to enroll children in RCTs, particularly those with a placebo control. In addition, the low prevalence of some pediatric conditions may make it difficult to recruit enough patients for a parallel group RCT. If recruitment is the limiting factor, extraction of more information from individuals or small groups of children using innovative designs and analyses may be necessary. The ultimate solution to the issue of small target populations is a multi-centre RCT. Observational studies are an option if experimental studies are not feasible, but they are preferable for studying safety as opposed to efficacy. While some of these alternative approaches may provide less rigorous evidence than large-scale parallel group RCTs, it is still preferable to have some form of evidence and to build a foundation for future research and clinical decisions than to avoid drug evaluation in children altogether, which may lead to the use of ineffective or unsafe medications.

Recent years have seen progress in dealing with the ethical and standardization challenges encountered when researching medications for children. Canada's nationally enforced policy on research ethics, the TCPS2, contains many references to children. However, as a broad document, it cannot address all of the relevant pediatric issues. The 2012 *Best Practices* document (discussed in Section 5.7.2) provides extensive supplementary guidance for Canadian investigators on longstanding and emerging ethical concerns in child health research (CGP & MICYRN, 2012). While guidance in other areas including study design and conduct is not as established, international initiatives such as StaR Child Health are working towards harmonizing pediatric research by developing uniform strategies for choosing age groups and outcome measures to use in studies for a particular condition (Hartling *et al.*, 2012b).

Research networks with the ability to facilitate multi-centre studies represent the ideal approach for studying drug efficacy in children. This has been demonstrated by the COG in the United States and the MCRN in the United Kingdom. The standardized protocols used by COG enable comparisons between studies, and the MCRN provides an infrastructure to support all aspects of clinical trials, from study design to recruitment, management, and closure. In addition to providing useful tools, these networks encourage a culture that supports pediatric research.

6

Monitoring and Studying the Safety of Pediatric Drugs

- Safety Monitoring and Studies
- Introduction to Post-Marketing Pharmacovigilance
- Methods for Signal Identification
- Methods for Assessing Risk and Mechanism
- Addressing Challenges in Monitoring and Studying Drug Safety in Children
- Towards an Integrated Approach to Post-Marketing Safety in Canada
- Chapter Summary

6 Monitoring and Studying the Safety of Pediatric Drugs

Key Findings

- Although common adverse drug reactions (ADRs) may be identified during pre-marketing clinical trials, detection of rare or unexpected ADRs often requires post-marketing collection and analysis of safety data (pharmacovigilance).
- The frequent lack of pre-marketing trials in children and consequent off-label use effectively means that drug safety in children is often assessed only in the post-marketing setting.
- Pharmacovigilance methods can be divided into identifying safety signals (preliminary indications of a potential ADR) and assessing risk and mechanism.
- Safety problems are signalled through post-marketing monitoring that tracks adverse events (passive and active surveillance and stimulated reporting), and through case reports in the literature. To interpret these signals (i.e., to determine whether drugs are causing ADRs and to calculate risk), evidence from controlled epidemiological studies is required.
- Although RCTs provide the strongest evidence for or against causal relations, many ADRs are rare and difficult to detect even for large multi-centre RCTs. Thus, observational studies are usually necessary to study drug safety in the post-marketing setting. In addition, use of specific algorithms and studies that evaluate biological mechanisms of an ADR also help to define causal relationships.
- Studying drug safety is more challenging in children for numerous reasons. Some of these challenges may be addressed by active surveillance programs that record comprehensive information in linkable databases and registries that can retrieve data concerning children; collection of long-term data to study less immediate ADRs that can have lasting effects; and improved reporting by physicians, even for ADRs that result from off-label use.
- Health Canada does not currently have the authority to require post-marketing studies, but has taken steps to encourage risk management plans for drugs and to establish networks for research in drug safety. Health Canada's counterparts in the United States and Europe have greater authority to request or require safety studies.

6.1 SAFETY MONITORING AND STUDIES

Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse events or any other possible drug-related problems” (WHO, 2002). While it is often viewed as the

monitoring of adverse events once medicines receive market authorization and are available to the public, pharmacovigilance can also involve safety studies before a drug is on the market and during clinical trials (HC, 2012g). Given that many drugs are not studied in children until they have already been marketed for adults, this chapter focuses on post-marketing pharmacovigilance and on the detection of rare adverse drug reactions (ADRs). The objectives of this chapter are to describe the main tasks involved in pharmacovigilance and to explore examples of initiatives or study designs for each;²³ to highlight advantages, challenges, and pediatric considerations for each type of approach; and to discuss specific challenges in monitoring and studying drug safety in children, along with some potential approaches for dealing with these challenges.

6.2 INTRODUCTION TO POST-MARKETING PHARMACOVIGILANCE

6.2.1 Distinction Between Pre- and Post-Marketing Safety Data

Before a drug is marketed, its safety is evaluated in non-clinical studies (e.g., *in vitro* and animal studies) and pre-marketing clinical trials. These studies can ensure that drugs will not induce serious ADRs in a large fraction of individuals; however, they reveal little about less frequent ADRs. Pre-marketing trials are generally performed with small and relatively uniform samples because their main objective is to efficiently demonstrate clinically important benefits; they are therefore useful only for detecting ADRs that occur with relatively high incidence (Vlahovic-Palcevski & Mentzer, 2011). Given that many serious ADRs occur with a cumulative incidence of 1 in 1,000 or less, they will not usually be detected before drug approval (Rieder, 2012). Furthermore, because more diverse and vulnerable populations, including children, are often excluded from pre-marketing study, fewer pre-market pediatric safety data are likely to be available (Etwel *et al.*, 2008). If children are excluded from *all* pre-marketing trials for a drug (an exception being vaccines research, in which children are nearly always included), any ADRs defined during those trials will be restricted to adults; ADRs affecting children taking the same drug may be very different (Iyasu & Murphy, 2007). The study of drug safety post-marketing therefore uses a wider variety of people and circumstances when compared to pre-marketing study (Vlahovic-Palcevski & Mentzer, 2011). Using these more widely applicable real-world situations, post-marketing study can lead to the detection of new, uncommon ADRs, especially in children, and the identification of ADRs that are unique to children, including those receiving drugs on- and off-label.

²³ The Panel uses the words *safety monitoring* to refer to all forms of monitoring and surveillance activities, including passive surveillance, stimulated reporting, and active surveillance. In contrast, the Panel uses the words *safety studies* to refer to observational studies and clinical trials. These activities are each discussed in detail in Section 6.2.

The distinction between off-label and on-label use is important for pharmacovigilance in children. Some post-marketing studies are designed to investigate only those safety signals that have arisen from on-label use (HC, 2011a). However, such studies are not always useful for pediatric drugs, since so many are prescribed without approval (excluding vaccines, which are not typically used off-label). Monitoring initiatives generally capture ADRs elicited by both on- and off-label drug uses, which makes them relevant for children, as long as the conditions and age groups for which the drugs are being used are recorded.

Post-marketing, the typical method for studying ADRs has been the collection of individual case reports of spontaneous adverse events from health professionals submitted to manufacturers and/or government drug regulatory authorities.²⁴ These reports then require analysis to assess the relationship between exposure to the drug and the subsequent occurrence of the adverse event to confirm (or refute) the hypothesized association, and to quantify any increased risks in both relative and absolute terms. In certain cases where there is widespread use of a product, as is the case with many vaccines, causal analyses may involve studies using large populations and information from large administrative health care databases (Velentgas *et al.*, 2012). Attempts are now being made to use more proactive approaches for monitoring and surveillance (Strom, 2005a), and these methods may be particularly useful for children. Other post-marketing studies may investigate the safety of a new drug formulation, or the safety of the same formulation in a new age group or a different sub-population (e.g., individuals with an underlying condition) (Millot *et al.*, 2011; Faye *et al.*, 2012; Palma *et al.*, 2012); all of these circumstances are highly relevant to children. Each of these approaches will be discussed further in this chapter.

6.2.2 The Current System for Pharmacovigilance in Canada

Although pharmacovigilance involves many players, an important regulatory role is identifying and acting on information about hazards and harms. Health Canada provides a system for reporting adverse events, to which consumers and practitioners can voluntarily submit information (HC, 2012g). In addition, manufacturers and distributors are required to provide Health Canada with any emerging information about safety (e.g., potential ADRs) or about efficacy (e.g., failure of the drug to produce the desired effect) following market authorization (HC, 2012g). Manufacturers submit annual summary reports that update the safety and efficacy profile of the product (HC, 2012g). Health

²⁴ Health Canada and the ICH both define an *adverse event* as “any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment” (ICH, 1994; HC, 2011a). Thus, the Panel uses the terms *adverse event* or *suspected ADR* to refer to reactions that have not yet been confirmed as definite ADRs.

Canada also conducts routine investigations of manufacturers by testing products in a lot release process (HC, 2001) and post-marketing regulatory compliance to ensure they are meeting reporting obligations (HC, 2012g). In addition, Health Canada works with public health partners at the federal, provincial, and territorial levels, and regulatory counterparts in other international jurisdictions (e.g., FDA, EMA), to share information and partner on pharmacovigilance activities (HC, 2012g).

When presented with sufficient evidence about questionable safety and efficacy of a product on the market (being used either on- or off-label), Health Canada can respond by (i) requesting changes to labelling, packaging, or manufacturing; (ii) stopping the sale of the product; or (iii) requesting a recall of the product (HC, 2001, 2012g). In many cases, Health Canada communicates the known and emerging risks through several channels to practitioners, manufacturers and the public as well as to regulators in other jurisdictions (HC, 2012g).

6.2.3 A Framework for Discussing Pharmacovigilance Through a Pediatric Lens

Pharmacovigilance research involves two main tasks: (i) signal identification, and (ii) assessing risk and mechanism (Figure 6.1).

A safety signal is a preliminary indication of a potential adverse reaction caused by a drug (HC, 2011d). A safety signal is formally defined as “a concern about an excess of adverse events compared to what would be expected to be associated with a product’s use” (FDA, 2005a). As discussed in Section 6.3, signals may arise from various post-marketing monitoring initiatives (e.g., passive surveillance, stimulated reporting, and active surveillance), which track alleged ADRs in databases, or they may be described as case reports or case series in the literature (another passive activity). Regulatory agencies are also working to refine various data mining tools with the goal of discovering signals in adverse event databases more quickly (see Section 6.3.5). Occasionally, investigators can assess which suspected cases meet the requirements for definite or probable ADRs based on individual cases (Kramer *et al.*, 1979). These decisions can be made less subjective by causality algorithms, which typically use a series of questions to determine the likelihood that a single event was caused by a drug. Causality algorithms are challenging to develop and many are not well-suited to children (Rieder, 2012). This issue is discussed further in Section 6.3.6.

Although signal identification is a crucial step in the study of ADRs, further analyses of safety signals using controlled studies with comparison groups are usually necessary to determine whether these signals truly represent a potential safety risk and to directly estimate the effect of drug exposure on increasing the risk of an adverse event (discussed in Section 6.4). In observational studies,

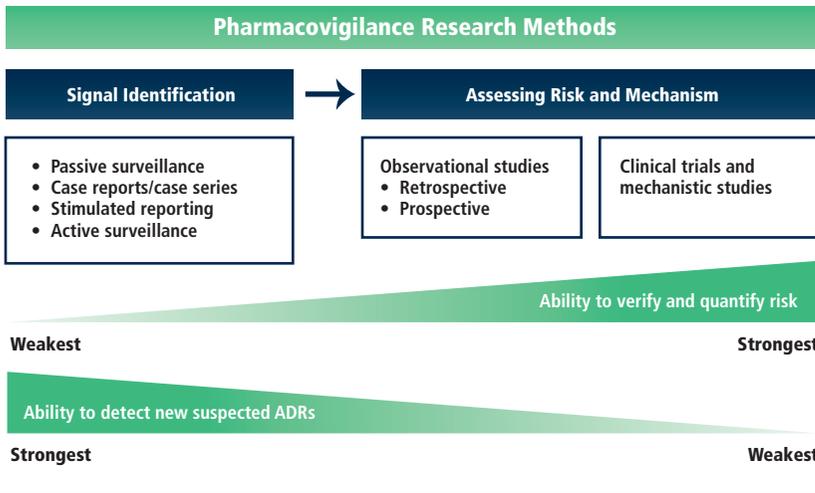


Figure 6.1

Pharmacovigilance Research Methods

Pharmacovigilance research involves two main tasks: (i) signal identification, and (ii) assessing risk and mechanism. Safety signals are generated by various post-marketing monitoring initiatives that track alleged ADRs in databases. Signals may also be described as case reports in the literature. These methods generate reports of exposed cases only, without corresponding controls, and are thus largely unable, on their own, to generate evidence for accepting or rejecting causal relations between drugs and suspected ADRs. However, causality algorithms can help to determine the likelihood that an individual event was caused by a drug and thus inform decision-making related to individual cases. To develop a more comprehensive picture of causality and risk, evidence from controlled studies (e.g., observational studies or trials) is required. These studies allow a direct estimate of the effect of drug exposure on the risk of an adverse event. Although experimental studies, such as RCTs, provide the strongest evidence for or against causal relations, the rarity of many ADRs makes it difficult even for large multi-centre RCTs to detect differences in adverse events in drug-exposed individuals. Note that in the context of this chapter, observational studies refer to opportunistic studies of real-world drug use (i.e., studies that observe the outcomes of patients who are taking drugs that have been prescribed by physicians on an individual basis), whereas clinical trials refer to experimental studies (i.e., studies that involve the assignment of participants to particular treatment groups by researchers based on a prospectively designed protocol).

investigators do not control the assignment of patients to treatment or non-treatment groups. Therefore, unlike RCTs, they cannot ensure that treated and untreated subjects are similar with respect to other factors that may affect the risk of the adverse event. RCTs provide the strongest evidence for or against causal relations. However, many ADRs are rare, making it difficult even for large multi-centre RCTs to detect differences in adverse events between groups. Thus, new ADRs are often best detected by monitoring initiatives and subsequently analyzed by large-scale observational studies. It should be noted that linear progression from ADR signals to causality studies is not always necessary. Other evidence (e.g., a possible ADR mechanism) may be sufficient to warrant further controlled study without waiting for signals.

Together, these methods help to develop a comprehensive picture of causality and risk. For example, the Vaccine Adverse Event Reporting System (VAERS), which is co-sponsored by the FDA and the Centers for Disease Control and Prevention (CDC), is regularly analyzed for signals suggesting previously unsuspected adverse vaccine reactions (VAERS, 2014). These signals can stimulate controlled observational (cohort) studies using large administrative health care databases to explore the relationship between exposure to the vaccine and subsequent occurrence of the adverse event. Such studies thus confirm (or refute) the hypothesized association between exposure and adverse event and quantify any increased risks in both relative and absolute terms.

The process of analyzing potential adverse reactions was illustrated by the reporting to VAERS of five cases of Guillain-Barré Syndrome (GBS) among adolescent recipients of the tetravalent meningococcal vaccine within 14 to 31 days of vaccination and within eight months of the vaccine's distribution in the United States. Follow-up cohort studies using multisite health plan administrative and claim data estimated the risk of GBS associated with the vaccine at 1.5 cases per 1,000,000 doses, that is, no increased risk of GBS following vaccination (Velentgas *et al.*, 2012). Estimating this relatively small level of risk was only possible through the large population studied and could not have been done during pre-market clinical trial testing. Further examples are explored in the following discussion.

6.3 METHODS FOR SIGNAL IDENTIFICATION

New ADRs are often first identified by the generation of post-marketing safety signals. Because these signals arise from clusters of individual cases once a drug is being used by large, diverse populations, they are sometimes able to detect ADRs that are particularly rare. The different methods for identifying safety signals generally include *passive surveillance*, *stimulated reporting*, and *active surveillance*. Signals may also emerge from case reports and published case series (another passive activity). All share one common limitation: they collect information only on individuals who experienced an ADR following exposure to the drug and not on those who did not experience an ADR following exposure or who were not exposed. Therefore, these signals must be analyzed further in order to make any definitive statements about causal relationships or relative risk.²⁵ Nonetheless, these methods represent an important component of the initial stages of a drug safety investigation, and it is important to understand the value, advantages, and challenges of each method.

²⁵ In the field of pharmacovigilance, *risk* is defined as the probability of harm being caused (i.e., the chance of an ADR occurring) and *relative risk* is the ratio of the risk in an exposed population and the risk in an unexposed population (WHO-UMC, 2013).

6.3.1 Passive Surveillance — Spontaneous Reporting

One mechanism for passive surveillance is spontaneous reporting from a practitioner, child, or parent regarding a suspected ADR. In a post-marketing context, a spontaneous report does not concern a product taken as part of a study or organized data collection initiative. Health Canada monitors ADRs through a passive surveillance system called the Canada Vigilance Program, which accepts ADR reports from manufacturers, practitioners, and consumers. Apart from mandatory reports submitted by manufacturers, the current system of monitoring ADRs in Canada is largely reliant on voluntary reporting (Carleton *et al.*, 2007; Castro-Pastrana & Carleton, 2011). An online database of these ADR reports (the Canada Vigilance Adverse Reaction Online Database) is searchable, with entries coded by ADR terms. The ADR reporting forms include a field for age, and the database may be searched using particular age limits, making it suitable for retrieving pediatric data. New information about ADRs is also made available in quarterly releases (HC, 2014b).

Spontaneous reporting can also be facilitated by specific public infrastructure; for example, in Canada, incidents following vaccination are monitored and assessed separately from the reporting of other ADRs. The immunization monitoring system includes several components: the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) (PHAC, 2012b); the Canadian Immunization Monitoring Program, ACTIVE (IMPACT) (CPS, 2012) (see Section 6.3.4); and the Advisory Committee on Causality Assessment (ACCA) (PHAC, 2012c). CAEFISS collects reports from public health authorities concerning reactions that might be associated with immunization. Information is forwarded to the federal Vaccine Safety Unit, which also monitors reports from vaccine manufacturers. Although otherwise similar to Health Canada's system for voluntary reports, health care providers in some provinces are required by law to report any potential adverse events following immunization (PHAC, 2012b). The United States has VAERS, a similar system for vaccine reporting that is also distinct from other ADR reporting (VAERS, 2014).

Advantages of Passive Surveillance

Reports from passive surveillance can signal rare reactions that were not detected in clinical trials (Carleton *et al.*, 2007). Spontaneous reporting is a relatively rapid and inexpensive surveillance method to generate signals that can indicate groups for further investigation, especially for rare but serious ADRs (WHO, 2007; Castro-Pastrana & Carleton, 2011). Spontaneous reports may reveal insights beyond the data provided in clinical and administrative records; for example, patient reports of ADRs have been shown to provide unique information not reported by practitioners (Blenkinsopp *et al.*, 2007). Spontaneous reports are also the only way to capture adverse reactions associated with use of

over-the-counter products, which are not included in prescription records (Lexchin, 2006). Hence, spontaneous reports represent unique signals of suspected ADRs.

Box 6.1 provides an example of a drug that is now contraindicated for children after publication of cases of ADRs using a database of spontaneous reports.

Box 6.1 **Adverse Drug Reactions Associated with Codeine Use in Children**

Codeine is used to treat pain in children and adults. As discussed in Chapter 3, polymorphisms in the gene encoding CYP2D6 can lead to variability in metabolism. As a result of this variation, poor metabolizers may receive ineffective relief and rapid metabolizers may produce high levels of morphine, which can lead to potentially fatal opioid-induced effects (e.g., respiratory depression) (Niesters *et al.*, 2013).

Serious concerns have recently been raised about the safety of codeine in children. In 2012, North American researchers reported a series of three life-threatening or fatal cases of opioid toxicity in children following codeine administration (Kelly *et al.*, 2012). The patients were all undergoing adenotonsillectomy for obstructive sleep apnea syndrome (OSAS). A similar case had been noted in Canada in 2009 (Ciszkowski *et al.*, 2009). Of these four cases, three of the children were ultra-rapid metabolizers. Since children with OSAS are already at risk for respiratory complications and surgery may not always resolve the condition, the treatment of these children with codeine may result in life-threatening respiratory depression (Kelly *et al.*, 2012). Other risk factors for elevated morphine levels include renal impairment (Niesters *et al.*, 2013) and being overweight (since doses are adjusted by weight and morphine accumulates minimally in fatty tissue) (Kelly *et al.*, 2012). Age-related factors (e.g., an immature blood–brain barrier) could create additional risk for children (MacDonald & MacLeod, 2010).

As a result of these concerns, and following a review of cases reported to their Adverse Event Reporting System, the FDA revised the label for codeine by adding a contraindication for treatment of pain in children after tonsillectomy or adenoidectomy (Kuehn, 2013). Health Canada now recommends codeine use only in patients aged 12 years or older (HC, 2013a), and a number of pediatric health care centres have removed codeine from their formularies in favour of morphine as a more predictable alternative (Wong *et al.*, 2012).

Challenges of Passive Surveillance

Until it is analyzed further (e.g., as a focus of a retrospective observational study), information from passive surveillance systems does not lend itself to comparing frequencies, distinguishing incidence, estimating absolute risk, or determining risk factors (Castro-Pastrana & Carleton, 2011; Härmark, 2012). Another important issue with the information gathered by passive surveillance is poor data quality. Records are frequently incomplete and often fail to report the outcome of the case (e.g., whether the patient died or whether any algorithm was applied to assess if the drug was causally related to the adverse event) (Carleton *et al.*, 2007). Forms can be submitted by medical and non-medical personnel, which causes variability in the quality of information. Furthermore, the diagnostic terms used by different physicians may vary (IOM, 1994). Another potential challenge is managing duplicate records. Several people may submit separate reports about a possible ADR in the same patient, and it may be possible to identify these duplicates within a database only by hand-searching (IOM, 1994). Lastly, the problem of under-reporting of ADRs in spontaneous reporting systems has been widely documented. A review of studies from 12 countries, including Canada, has estimated the median under-reporting rate to be 94% depending on the setting, and concludes that under-reporting is significant and widespread even for more serious and severe ADRs (Hazell & Shakir, 2006). The lack of reporting under a passive surveillance system can thus lead to major gaps in the data used to monitor safety.

Other challenges in passive surveillance relate to collecting and managing data. Health Canada has guidelines that direct the use of information from various sources for regulatory decisions (HC, 2003). A recent audit noted that Health Canada relies upon a resource-intensive process for warehousing reports of ADRs, which may have limited its ability to identify, monitor, and manage risks. That report noted, in particular, under-use of adverse event reports from foreign jurisdictions in national pharmacovigilance monitoring (OAG, 2011). This evidence suggests that, in addition to data quality issues (i.e., inaccurate, incomplete records), barriers to consolidating information from multiple sources may obscure signals.

6.3.2 Case Reports and Case Series

Medical literature that describes the details of a single adverse event, or a series of occurrences in the form of published case reports or case series, is an additional source of signalling previously unknown ADRs. In fact, many new ADRs are first identified in scientific papers (Stricker & Psaty, 2004; Etwel *et al.*, 2008). A single well-documented case report can be viewed as an ADR signal, particularly if it describes aspects such as patient characteristics (e.g., use of concomitant medications or underlying medical conditions); the

patient's previous experience with the drug; the time-course of the adverse event relative to drug administration; a mechanistic explanation; clinical and laboratory manifestations; and the results of *dechallenge* (drug discontinuation) and *rechallenge* (re-administration) (FDA, 2005a).

Advantages of Case Reports and Case Series

Case reports typically provide a higher level of detail than spontaneous reports submitted to surveillance databases. In addition, since they are published in scientific journals, they are assessed for quality by peer reviewers (Stricker & Psaty, 2004). The reports also have the advantage of an immediate audience; thus, unlike spontaneous reports collected by monitoring initiatives, which may remain unanalyzed for years, case reports in the literature may be read by others who have witnessed similar adverse events. Although insufficient to determine causation, a well-documented case or series of cases may provide enough evidence to issue a warning for a drug, particularly if the ADR is life-threatening (see Box 6.1).

Challenges of Case Reports and Case Series

As with all adverse events reported to monitoring systems, case reports do not necessarily represent true ADRs (Stricker & Psaty, 2004). Since they are published before undergoing epidemiological analyses, they can lead to premature concern and confusion in the general public, particularly if they are sensationalized by the media, which occurred with reported adverse events following administration of the measles, mumps, and rubella (MMR) vaccine (Deer, 2011; Godlee *et al.*, 2011).

6.3.3 Stimulated Reporting

Methods to encourage and facilitate reporting, referred to as stimulated reporting, can increase the flow of information on drug safety. The stimulus might come from a sponsor or company or from a central authority or investigator. Stimulated reporting can involve increasing the motivation to report by highlighting relevant safety information, encouraging caution in use, and providing a pre-designed channel for reporting (WHO, 2007). Product labels, for example, can be used to communicate risks and also reinforce the importance of reporting any adverse reactions related to medication use (Lexchin, 2006; Rawson, 2013; Senate, 2013).

Reporting can also be stimulated with direct inquiries. For example, the Canadian Paediatric Surveillance Program (CPSP) monitors rare severe pediatric diseases and conditions. Participating practitioners are contacted monthly to report on the number of cases they observe and fill out a detailed questionnaire on each case. In 2004, the CPSP launched an ongoing study on ADRs by asking

CPSP participants to submit reports on any serious and life-threatening ADRs that they encountered. The CPSP confirms cases of adverse reactions with follow-up to identify the products associated with the reactions and the types of reactions, as well as to distinguish which reactions had not previously been reported to the national Canada Vigilance Program (CPSP, 2009; Zimmerman, 2012). The CPSP publishes its results in annual reports that summarize the classes of medicines most frequently suspected of causing ADRs for the given year (CPSP, 2013). Causality analysis is not the primary objective of the CPSP and is generally not completed in its annual reports or in any specific ADR surveys it conducts (CPSP, 2009). Nonetheless, the CPSP represents a valuable source of pediatric-specific data that can be used for further research.

Advantages of Stimulated Reporting

Compared with data from administrative records — hospitalizations, insurance billing, or laboratory results — stimulated reports are more timely (Ugnat *et al.*, 2011). A major advantage of stimulated reporting programs such as the CPSP is their ability to generate more standardized, complete records. According to the quality grading scale used by the WHO, the quality of clinical information gathered by the CPSP is considered to be good to excellent (Zimmerman *et al.*, 2011). Other studies have also measured improvements in ADR report quality following various interventions (Pedros *et al.*, 2009; Johansson *et al.*, 2011).

Challenges of Stimulated Reporting

Providing stimulated reporting programs can require a significant resource investment (e.g., dedicated personnel and infrastructure) (Carleton *et al.*, 2009). Any provided stimulus must also overcome any real or perceived inconvenience or burden of providing reports (Ugnat *et al.*, 2011; Zimmerman *et al.*, 2011). Despite external encouragement, stimulated reporting is vulnerable to the same shortcoming as passive surveillance, namely, selective responses and incomplete information (WHO, 2007). In addition, incentive and educational schemes are often short-lived, and increases in reporting do not persist when the incentives are withdrawn (McGettigan *et al.*, 1997; Figueiras *et al.*, 2006).

6.3.4 Active Surveillance

Active surveillance systems involve a process for soliciting information that is more organized and continuous than that of passive mechanisms (WHO, 2007). Active surveillance can involve follow-up through one of several channels, such as chart review or interviews of a sample of sentinel sites, contact with patients or practitioners based on prescription records, or investigation of data in a disease registry. Many active surveillance initiatives are specific to hospital settings, and most involve additional human resources or infrastructure dedicated to the monitoring effort. Compared to passive and stimulated surveillance systems,

which often do not successfully capture specific or standardized information, active surveillance involves more complete information on patient and exposure characteristics (WHO, 2007).

There are a range of approaches to active surveillance, some of which involve actively researching adverse events (or potential risks identified in previous research) through multiple existing datasets (e.g., using sentinel site information), while others focus more intensely and deliberately on combining knowledge from existing data with the knowledge gained through the collection of new and continuous information over time (e.g., creating and using patient registries).

Using Sentinel Site Information

One type of active surveillance is ongoing participation of a sample of sites or practitioners. In this type of monitoring, information on medicine use can come from chart reviews — manual or electronic — or from interviews with and reports from individual patients and practitioners. The data from this method can be more complete than those from passive surveillance, often with more reports on specific subgroups. In this way, sentinel monitoring can allow the targeting of resources to follow up on priority issues (WHO, 2007; Matlow *et al.*, 2011).

The FDA has been experimenting with active post-marketing surveillance through its Sentinel Initiative, a system for using existing databases from multiple sources to monitor FDA-approved drugs and medical products. In the sentinel model, the data remain in the original environment rather than being consolidated centrally, but the analytical priorities stem from central direction. The coordinating centre processes questions on drug safety from the FDA and develops analytical programs that are used by the partners to query the data. Data partners provide summary information to the coordinating centre and to the FDA (FDA, 2010b). The program met an initial goal of covering 25 million people by 2010.

The sentinel model improves upon traditional post-marketing surveillance in several ways. The monitoring is near real-time, more current than traditional paper-based and passive reporting. Drawing from both electronic medical claims and administrative health care data, the sentinel model provides more comprehensive coverage than monitoring in single settings such as hospitals. And, by drawing on many data sets, the model generates sample sizes large enough to examine special populations that might otherwise be too small for meaningful analysis (FDA, 2010b). However, the sentinel model also has several limitations for monitoring drug safety in children. In particular, the data sets

on which it is constructed are not highly focused on pediatrics, and coding systems within the databases are designed for adults rather than children (see Table 6.2).

Creating and Using Patient Registries

Another example of the many approaches to active surveillance is the use of *patient registries* — an organized system for collecting patient information in a uniform manner over time. Registries can be used to evaluate specified outcomes within populations who have certain health conditions or risk factors (disease registries), or who are receiving certain health products or services (medicine registries) (WHO, 2007; AHRQ, 2010). Disease registries can be used to compare patients within the registry receiving different treatments, patients with different conditions within the registry, or patients within the registry with those in another comparable registry. Alternatively, medicine registries can look at varying populations exposed to a given medicine over time. Although many registries are used to describe the natural history of a disease, determine clinical effectiveness, and measure quality of care, given that they actively capture all treatment outcomes (either positive or negative) registries are also extremely relevant for measuring and monitoring adverse events (AHRQ, 2010).

Registries aim to address goals that are well defined before any collecting or analyzing of data takes place, and they do not rely solely on data available in an existing dataset (i.e., certain information is often collected solely for the purpose of the registry). Registry data are standardized (i.e., are specific, have clear definitions, and are collected with uniform frequency and manner), comprehensive, and reflective of the information needed for appropriate clinical decision-making (AHRQ, 2010). Registries are therefore extremely relevant for capturing and reporting on adverse events involving children, especially when created for child-specific conditions. For example, the Canadian Cystic Fibrosis Registry maintained by Cystic Fibrosis Canada was created in the early 1970s. The registry captures comprehensive and ongoing information from 42 health care facilities across Canada with the goal of monitoring trends in disease patterns and care over time. The data collected within the registry are used to develop better care options and respond to emerging issues; they are extremely relevant for detecting any adverse events related to established or new cystic fibrosis medicines used in children (CFC, 2014).

The biggest limitation of registries is the extent to which they capture a given population. Although registries are useful for a particular disease or treatment, they would not be able to capture ADRs across a more broadly defined population. As such most children receiving drugs would not be captured in such a system.

A Promising Canadian Example: IMPACT (Immunization Monitoring Program, ACTIVE)

In Canada, an example of a pediatric-specific active surveillance initiative is IMPACT, a hospital-based surveillance network that tracks potential adverse events following immunization. IMPACT involves 12 Canadian children's hospitals and health centres, each with a dedicated staff member who forwards reports to CAEFISS (see Section 6.3.1). The system is designed to actively collect information on any events requiring hospitalization that are temporally related to immunization. The staff member also serves as a link if more information is requested by the ACCA, which analyzes the most severe or unexpected adverse events following immunization (CPS, 2012).

Advantages of Active Surveillance

Active surveillance is more conducive to interaction between regulatory agencies and clinicians than passive surveillance. Dedicated staff members can communicate specific safety concerns to regulators in a timely manner, and data collection programs can be adjusted as needed, based on new safety information from the regulator (Castro-Pastrana & Carleton, 2011). Active surveillance is especially suited to institutional or clinical settings with established infrastructure for record-keeping; monitoring can also use existing networks of practitioners (Ugnat *et al.*, 2011). Reports generated with these methods of monitoring can provide more details related to both the drug and the reactions, such as time of onset, duration, and health outcomes (Carleton & Smith, 2005). When data collection is standardized, datasets can be linked — across institutions or regions, for example — to increase the sample size and thus permit more in-depth analysis (Castro-Pastrana & Carleton, 2011). With more complete and numerous records, data from active surveillance can build understanding about contributing factors such as drug classes associated with adverse events (Matlow *et al.*, 2011).

Challenges of Active Surveillance

Any active method of monitoring requires resource investment, such as dedicated personnel and infrastructure for follow-up of cases, and therefore associated costs (Carleton *et al.*, 2009). Active surveillance initiatives are generally more targeted than passive monitoring (e.g., IMPACT only collects hospital data) and thus may be more useful to those working in institutional settings as opposed to other real-world contexts. However, if the information is fed into other, more comprehensive databases or combined with information gleaned from passive surveillance activities, it can be considered as part of a larger and more comprehensive evidence base (e.g., IMPACT data is forwarded to CAEFISS and ACCA to complement other surveillance data).

6.3.5 Discovery of Potential Adverse Drug Reactions Using Data Mining Algorithms

Data mining refers to “the use of computerized algorithms to discover hidden patterns of associations or unexpected occurrences (i.e., ‘signals’) in large databases” (Almenoff *et al.*, 2005). The associations are based purely on the frequency with which drugs and events are reported together; therefore, the results of data mining can help to generate hypotheses, which should then be investigated further in the context of other available data. This technique provides a systematic approach for analyzing, in a timely and consistent fashion, the abundance of information contained in large post-marketing drug safety databases (Almenoff *et al.*, 2005).

Two common statistical techniques for data mining are Bayesian methods and methods that generate *reporting ratios*, both forms of *disproportionality analysis*. In the former, algorithms are used to generate *signal scores* for drug–event pairs, which represent the strength of a reporting association. Scores can also be computed for adverse events resulting from drug combinations. This technique identifies consistent, replicable signals and minimizes random patterns (Szarfman *et al.*, 2002; Almenoff *et al.*, 2005). The latter technique generates a ratio that compares how often the drug–event pair is mentioned in adverse event reports to how often it would be expected, if mention of the drug and event were statistically independent of each other (Almenoff *et al.*, 2005). *Multivariate modelling* algorithms (e.g., logistic regression) are also being evaluated (Harpaz *et al.*, 2013). A key consideration when applying these algorithms is finding an appropriate balance between *sensitivity* (the ability to detect true ADRs) and *specificity* (the ability to correctly identify the absence of ADRs) (Cochrane Collaboration, 2013; Harpaz *et al.*, 2013).

An analysis of various signal detection algorithms using data from the FDA Adverse Event Reporting System (FAERS) suggested that most are reasonably accurate at predicting ADRs and separating them from associations that are likely false (Harpaz *et al.*, 2013). In this study, multivariate models were superior to those based on disproportionality analysis; at a pre-defined level of sensitivity, they provided better specificity. Because the multivariate approach requires advance selection of predictors (e.g., drugs and covariates such as age) to be included within the model, it may be advantageous for pediatrics. However, this approach involves more complex modelling decisions, and can therefore be slower to compute.

The EudraVigilance database (initiated by the EMA) has also been analyzed to test the value of data mining. In one study that used a reporting ratio method, 54% of signals designated as important medical events were detected earlier using an algorithm than they were using standard pharmacovigilance procedures such as Periodic Safety Update Reports (PSURs). In the cases where faster detection is possible, the authors estimated that data mining algorithms could avoid a mean delay in detection of 2.45 years. However, the study emphasized that many signals are first identified by active surveillance, reviews, clinical trials, and PSURs, so data mining should be considered a method to support standard pharmacovigilance activities (Alvarez *et al.*, 2010).

Some significant challenges arise when attempting to assess the performance of data mining algorithms. First, an objective measure of what constitutes a true causal relationship (i.e., a gold standard) is lacking. Second, sensitivity and specificity can be increased only at the expense of each other, and there are no defined critical values for these parameters. Without these standards, it is difficult to accurately and consistently evaluate the sensitivity, specificity, and predictive value of signal detection algorithms. In addition, it is challenging to weigh the costs (e.g., effort required to perform analyses and investigate signals that are potentially false positives) and benefits (e.g., positive impact on public health) of data mining (Almenoff *et al.*, 2005; Alvarez *et al.*, 2010).

6.3.6 Assessing Causality in Individual Adverse Event Cases

Causality algorithms can be used to analyze the likelihood that a single adverse event in one individual is drug-related. These algorithms lead the investigator through a series of questions about the event itself (e.g., whether the event may have been caused by an underlying disease or whether the event improved after the drug was stopped and worsened after the drug was re-administered) and any background information that may be valuable (e.g., whether there is any evidence to support a causal mechanism or whether similar events have been described previously). Algorithms may take the form of a series of questions with a numerical value attached to each answer or a flow chart. Based on the total score or the final position in the chart, ADRs are categorized as unlikely, possible, definite, or probable (Rieder, 2012). In some cases, the adverse event may occur so suddenly and with such severity that associations may be more clearly labelled as probable causal relationships. A classic example is immediate allergic reactions to betalactam antibiotics such as penicillins and cephalosporins (Atanaskovic-Markovic *et al.*, 2005; Novembre *et al.*, 2009). Other associations may be much less clear.

The most well-known and commonly accepted algorithm for establishing causality are the Bradford Hill criteria, a set of questions used to characterize aspects of an association to help interpret that association as likely to be a causal relationship (Hill, 1965). They include questions related to strength, consistency, specificity, temporality, biological gradient, plausibility, and coherence. The Bradford Hill criteria have been applied to pharmacovigilance assessments (Shakir & Layton, 2002; Perrio *et al.*, 2007) and have been used by regulators in assessing adverse events resulting from vaccines (NVAC, 2010). Building on the work of the Council for International Organizations of Medical Sciences (CIOMS) and a CIOMS/WHO Working Group, WHO also has a manual that includes a checklist and algorithm for assessing causality of adverse events following immunizations that uses similar criteria (CIOMS, 2012; WHO, 2013b).

Causality algorithms have several advantages. In addition to assessing causality in individual cases, causality algorithms can also help to inform future epidemiological studies. If an algorithm suggests that several adverse event cases indicate a probable new ADR, large-scale epidemiological studies may be conducted for further analysis. Better causality assessment tools may help with individual patient care and clinical decision-making as well as safety monitoring in health care settings. User-friendly algorithms may aid clinicians in making rapid decisions about whether or not drug therapy should be continued. Standardized procedures for monitoring, analyzing, and documenting adverse events may help to identify ADR triggers (Du *et al.*, 2012; Rieder, 2012).

Valid and consistent causality algorithms are challenging to develop. They have been criticized as lengthy and time-consuming, incomplete, at times applicable only to specific organ toxicities, arbitrary in their scoring system, and potentially invalid and unreliable in the pediatric setting (Du *et al.*, 2012). A commonly used algorithm is the Naranjo algorithm, which was developed to assess ADRs in adult patients treated with neurotropic drugs (Rieder, 2012) but was intended to be applicable to a variety of clinical situations (Naranjo *et al.*, 1981). Some newer causality assessment tools have demonstrated improved inter-rater reliability and greater validity than the Naranjo algorithm (Gallagher *et al.*, 2011; Du *et al.*, 2012). One of these was developed using patient data from a neonatal intensive care unit, with the goal of creating a tool that would be more reliable for evaluating possible ADRs in infants (Du *et al.*, 2012). Although algorithms have the potential to contribute to individual care and to establish an individual event as related to a drug, this type of analysis does not help to determine the effect of drug exposure on increasing the risk of an adverse event at the population level.

6.3.7 Prediction of Adverse Drug Reactions Using Mathematical Modelling

An unavoidable drawback of monitoring and surveillance methods is that patients must experience unpleasant and potentially dangerous adverse events before data can be collected and patterns can be recognized. New computational network approaches are currently being developed to predict suspected ADRs from existing data on known ADRs (e.g., from adverse event monitoring databases), intrinsic drug properties, protein targets of drugs, and known drug–drug or drug–disease interactions (Atias & Sharan, 2011; Cami *et al.*, 2011; Huang *et al.*, 2011; Cami *et al.*, 2013). Previous statistical methods for detecting such safety issues relied on analysis of post-marketing data accumulated over many years, often only after numerous people experienced an adverse event (Cami *et al.*, 2013). These novel mathematical models have the potential to predict ADRs earlier, possibly even before human trials are conducted (Cami *et al.*, 2011; Huang *et al.*, 2011).

Typically, this method of predictive modelling involves constructing a complex network with hundreds of *nodes*, each signifying a specific drug or a specific class of ADR, with the connections between them representing either a drug–ADR association or a drug–drug interaction. Cami and colleagues developed two novel modelling approaches: one for drug–ADR associations, known as a Predictive Pharmacosafety Network (PPN), and one for drug–drug interactions, called a Predictive Pharmacointeraction Network (PPIN) (Cami *et al.*, 2011; Cami *et al.*, 2013). They tested the performance of each by comparing the model’s predictions with new safety information that became available from the same database used to construct the model. Both models showed that network-based methods could be useful for predicting unknown ADRs. Although mathematical modelling has not been widely used for pharmacovigilance, it could be applied to other areas, such as vaccination, in which it is difficult to determine the probability of very rare ADRs. A limitation of predictive ADR modelling for pediatrics is its reliance on large volumes of existing data, which are currently lacking for children.

6.4 METHODS FOR ASSESSING RISK AND MECHANISM

In order to make definitive statements about the causal relation between a drug and an adverse event, safety signals must usually be analyzed from controlled studies, allowing a direct estimate of the effect of drug exposure on the occurrence of an adverse event. Controlled observational studies permit the calculation of relative risk by comparing the rate of occurrence of an adverse event in exposed versus non-exposed individuals (IOM, 1994). It may be possible to perform these studies retrospectively if data from exposed and non-exposed individuals are available (e.g., from health services databases as

discussed in Box 6.5). It is also important to study biological mechanisms of ADRs; a proven or plausible ADR mechanism strengthens the evidence of a causal relationship between a drug and an ADR (see Section 6.4.3).

6.4.1 Motives for Post-Marketing Studies

Post-marketing studies may be undertaken for various reasons. As discussed, they are often carried out to investigate safety signals that arise from spontaneous reports. Box 6.2 provides an example of the manner in which a safety investigation may progress, from spontaneous reports to controlled observational studies.

Box 6.2

Potential Association Between Leukotriene-Modifying Agents and Suicidal Behaviour in Children

Asthma is a common chronic condition requiring pharmacotherapy that affects approximately 10% of two- to seven-year-old children in Canada (Thomas, 2010; Asthma Society of Canada, 2014). Montelukast (Singulair®) is a leukotriene-modifying agent (LTMA) used as an oral alternative to corticosteroids to help control asthma (Schumock *et al.*, 2012). In 2008, the FDA issued a warning about a possible association between montelukast and “behaviour/mood changes, suicidality (suicidal thinking and behaviour) and suicide” (FDA, 2008). Product monographs for Singulair® were updated in both the United States and Canada to include these psychiatric disturbances as possible ADRs (HC, 2009b). The FDA warning was later extended to other LTMA (FDA, 2009c).

The FDA began its safety review by requesting manufacturers of LTMA to submit data on adverse events related to suicidality and other mood or behaviour changes from previously completed placebo-controlled clinical trials. A total of 97 clinical trials (involving 19,214 patients who received an LTMA and 13,502 who received a placebo) revealed three instances of suicidality, two of which occurred in placebo-treated patients (FDA, 2009b). In 2009, Merck® Research Laboratories published its pediatric safety data for montelukast collected from a series of double-blind placebo-controlled trials and open-label extension studies. One case of suicidality was identified in a 12-year-old patient receiving open-label montelukast, but the incident was considered unrelated to the drug (Bisgaard *et al.*, 2009). None of these data suggested an association between LTMA and suicidality.

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Subsequently, a search of the literature and the FAERS revealed 838 LTMA-associated cases of suicide-related adverse events. While this number seems alarming, almost all of the cases (96%) occurred in 2008 and 2009, after the FDA warning, suggesting that the dramatic increase may have been influenced by the warning (Schumock *et al.*, 2011). Similarly, 12 of the 13 ADR reports submitted to Health Canada associating suicidality or self-injury with montelukast occurred after the FDA warning (HC, 2009b). Finally, in 2012, the first large-scale observational study (using a case-control design) was completed to analyze the association between LTMA and suicide attempts in children and young adults. While no association was found, the study suggested an increased risk in patients aged 19 to 24 years and suggested a need for further research (Schumock *et al.*, 2012).

The current American and Canadian labels for Singulair® include a warning about possible neuropsychiatric events, but the drug is not contraindicated for children (Merck & Co. Inc., 2012, 2013). In addition to a lack of clear evidence suggesting an association between LTMA and suicidality, there is no clear pharmacological mechanism to explain how LTMA could cause neuropsychiatric effects (Schumock *et al.*, 2011).

In addition to investigating safety concerns, post-marketing studies may also be conducted:

- *As a condition of market authorization* — An example of this situation is the requirement for pediatric studies under the *Pediatric Research Equity Act* (PREA) in the United States; a drug may be granted authorization under the condition that pediatric studies will be completed during the post-marketing phase (FDA, 2005b).
- *To investigate the safety and efficacy of an unauthorized use* — Studies may be conducted with marketed drugs to investigate their use for a new condition, age group, or sub-population (e.g., people with an underlying condition such as AIDS or renal failure), or to test the safety and efficacy of a new formulation or dose (FDA, 2009a).
- *As part of ongoing regulatory safety reviews* — Established in 2002 under the BPCA and expanded in 2007 under PREA, the FDA required a safety review of a drug one year after being authorized for use in children. In 2012, as legislated by the *FDA Safety and Innovation Act*, this review period was extended to 18 months (U.S. Congress, 2012). Overseen by the Pediatric Advisory Committee, this process involves a review of data from original trials, trends in use of the drug by adults and children, any reported adverse events, product

labelling, and other published clinical, pharmacological, and statistical information. Since 2003, the majority of these reviews have indicated no apparent safety concerns, but in some cases there have been recommendations to change the label to better highlight potential safety issues. For example, safety concerns have been raised with certain psychiatric medications, proton pump inhibitors, and solutions using alcohol and propylene glycol (IOM, 2012b; Murphy *et al.*, 2014).

6.4.2 Regulatory Requirements and Incentives for Post-Marketing Studies

Health Canada does not have the authority to require post-marketing studies (HC, 2011b), which raises questions about the instigation of these studies in Canada. In the absence of regulatory incentives for post-marketing studies, the Government of Canada is funding this research through the Drug Safety and Effectiveness Network (DSEN), a CIHR-hosted initiative to increase and improve the study of marketed drugs (described in Box 6.3).

Box 6.3 **Drug Safety and Effectiveness Network**

To meet a recognized need for post-marketing real-world drug studies, Health Canada and the CIHR established the DSEN in 2009. DSEN is made up of virtual teams linking more than 150 researchers connected with existing data centres (Peterson, 2012). To date, DSEN teams have approximately 100 active or completed projects (DSEN, 2013), 11 of which focus on pediatric use of drugs (Peterson, 2012). DSEN investigations are directed by requests from drug plan managers, federal-, provincial-, and territorial-level policy-makers, health technology assessors, and Health Canada (Senate, 2013). With expertise and capacity in such methods as active surveillance, observational studies, prospective comparative effectiveness research, pharmacogenomics of ADRs, and network meta-analysis, DSEN teams are a resource for evidence on post-marketing safety and comparative effectiveness for health care decisions.

One of the seven DSEN teams is the Canadian Network for Observational Drug Effect Studies (CNODES), whose main aim is “to use collaborative, population-based approaches to provide rapid answers to questions about drug safety and effectiveness” (CNODES, 2013). CNODES has access to the administrative health and prescription records of over 40 million people, which include data from seven Canadian provinces as well as information in the U.K. General Practice Research Database and the U.S. MarketScan database (Filion *et al.*, 2014). By using large datasets and epidemiological study methods, CNODES has the capacity to detect rare adverse events and to estimate the benefits and risks of medications (CNODES, 2013).

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CNODES has yet to investigate adverse drug events in children. CNODES relies on data from publicly funded provincial and federal health plans. Because many children are not covered by provincial drug plans, and since those plans vary considerably in eligibility as well as in the drugs covered (Ungar & Witkos, 2005), CNODES may have limitations for pediatric studies; however, there is still the potential for such work. In addition to responding to decision-maker queries, DSEN has launched two funding opportunities that specifically target pediatric drug safety and effectiveness research (Peterson, 2012).

DSEN does not directly support studies proposed by individual investigators, the public, for-profit enterprise, or voluntary organizations (Senate, 2013); instead, it focuses on the needs of decision-makers (Peterson, 2012). Pediatric investigators may therefore find their topics of interest left unaddressed unless they are considered to be informative to current priority considerations by Health Canada or other high-level decision-makers. Nonetheless, the DSEN Scientific Advisory Committee does provide a forum for DSEN researchers to table those topics that are, in their judgment, feasible and address research gaps (DSEN, 2013). Several examples of successful queries have followed this route (e.g., a proposal to examine genetic profiles leading to higher response rates and lower adverse events following the use of newer hepatitis C drugs). DSEN-funded research is designed to meet the needs of regulators and provincial decision-makers that provide access to medicines, thereby providing a direct avenue for the uptake of evidence to aid in regulatory and listing (payment) decisions (DSEN, 2013).

6.4.3 Evaluating a Potential Causal Mechanism

One of the questions that investigators may want to answer, either by using case reports or controlled epidemiological studies, is whether the evidence supports a causal mechanism for an ADR (Gallagher *et al.*, 2011). In other words, is any information available to explain the potential biological process that causes the ADR (i.e., *why* and *how* it occurs)?

Some ADRs have well-characterized biological mechanisms. For example, immune-mediated ADRs, while generally uncommon, are frequent causes of serious and life-threatening ADRs (Rieder, 2012). Other potential ADRs do not have a known mechanism but remain *biologically plausible*, which indicates that “a knowledgeable person could postulate a feasible mechanism” by which the medicine could cause the adverse event (IOM, 1994). See Box 6.1 for an example of a potential ADR *with* an apparent biologically plausible mechanism

and Box 6.2 for an example of a potential ADR *without* apparent biologic plausibility. *Demonstrated* biologic plausibility implies that the ADR mechanism has been confirmed by *in vitro* or animal studies (IOM, 1994).

ADRs can be caused by variations in the genes that encode proteins such as drug-metabolizing enzymes. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is exploring this phenomenon. The CPNDS — originally called the Genotype-specific Approaches to Therapy in Childhood (GATC) project — involves dedicated surveillance clinicians in 12 pediatric hospitals across Canada (Carleton *et al.*, 2009; CPNDS, 2012). At each site, physicians, pharmacists, and nurses collaborate to “identify, enroll, and collect clinical data and biological samples from patients who experience ADRs as well as patients who receive the same medication without an ADR (controls)” (Carleton *et al.*, 2009). Samples are genotyped, allowing researchers to identify genetic differences between cases and controls that may be associated with an ADR (Carleton, 2010). Using this case-control methodology, the CPNDS successfully identified genetic factors causing hearing loss induced by cisplatin (a widely used chemotherapeutic agent) (Ross *et al.*, 2009), codeine-induced opioid toxicity in breastfed infants (Madadi *et al.*, 2009), and cardiotoxicity induced by anthracyclines (also used for chemotherapy) (Visscher *et al.*, 2012; Visscher *et al.*, 2013).

6.4.4 Establishing a Post-Marketing Study Design to Assess Risk

The Panel has chosen to divide post-marketing studies into *retrospective* studies (those that use existing information, such as data collected by monitoring initiatives) and *prospective* studies (those that rely on the generation of new data). Prospective studies may be observational studies (which do not involve the assignment of a participant to a particular treatment) or controlled (usually randomized) trials. Both of these study types may be initiated voluntarily or mandated by the FDA or EMA (but not Health Canada) (FDA, 2011; HC, 2011b; EMA, 2013f).

RCTs are the most convincing design for both efficacy and safety studies. Because they use random assignment, they are the least likely to be affected by confounding variables and therefore the most likely to identify associations that are truly causal (Strom, 2005b). However, this does not necessarily make them the most practical choice for a post-marketing safety study. If the purpose of the study is to demonstrate efficacy (e.g., for testing a new formulation in a new age group), then an RCT is indeed appropriate (IOM, 2012a). If the purpose is to study a potential ADR that is thought to be rare, however, an RCT is likely to be too expensive, logistically difficult, and time-consuming because it would require an unfeasibly large sample size. It may not be appropriate to address urgent safety concerns with the delay that RCTs necessitate (Strom, 2005b). The suitability of a given study design depends on the study objectives.

In some instances, multiple study types may be involved in the investigation of a single drug. The process may progress from case reports to retrospective observational studies and, if necessary, large-scale prospective studies. The level of evidence required may depend on the importance and uniqueness of the drug and the severity and frequency of the ADR. If similar drugs are available and the ADR is life-threatening, the drug may be more readily withdrawn from the market or contraindicated for a specific population, even without the robust evidence of a prospective post-marketing study — see Box 6.1 for an example (Strom, 2005b). However, a complete, robust picture of causality and risk will only be obtained if epidemiological studies or RCTs are conducted.

Table 6.1 reviews some of the advantages, disadvantages, and pediatric considerations for each type of post-marketing study design.

Table 6.1
Considerations for Various Post-Marketing Study Designs

Study Type	Advantages, Disadvantages, Pediatric Considerations	Pediatric Example
Retrospective observational (using existing data) <ul style="list-style-type: none"> Data on the population of interest are extracted from existing information sources. Individuals are compared based on the presence or absence of an ADR or the presence or absence of exposure to a drug. Goal is to determine whether exposure to certain drugs can be associated with specific ADRs. 	Advantages <ul style="list-style-type: none"> Use of existing information may allow for the generation of results quickly and inexpensively. Particularly helpful for rare ADRs, which may require a long delay to study prospectively. Disadvantages <ul style="list-style-type: none"> Quality of existing records may be poor (incomplete, inaccurate, or unclear). May be difficult to find existing information on comparison groups. Less likely to account for all sources of bias. Pediatric considerations <ul style="list-style-type: none"> Databases may not be set up for retrieval of pediatric data (see Section 6.5). 	<ul style="list-style-type: none"> A retrospective observational study to determine the risk of Guillain-Barré syndrome (GBS) following immunization with a meningococcal conjugate vaccine (MCV4). Among 12.6 million children aged 11–21 years, over 1.4 million were vaccinated with MCV4 between March 2005 and August 2008. None of the 99 confirmed cases of GBS occurred within 6 weeks of vaccination, yielding an incident rate of 0. (Velentgas et al., 2012)
Prospective (creating new data) <ul style="list-style-type: none"> Population at risk for experiencing an ADR is followed over time. Comparison cohort often chosen based on different level of exposure to product (e.g., no exposure or exposure to different dose). 	Advantages <ul style="list-style-type: none"> Data are more likely to be of higher quality (more detailed, complete and accurate) than retrospective data. Exposure data (and other information) can be tracked at every visit during follow-up using standardized procedures, which facilitates generation of a rich dataset and simplifies group-to-group comparisons. Disadvantages <ul style="list-style-type: none"> May take many years to complete. Less likely to account for all sources of bias. May be difficult to recruit enough exposed children to enable the study of rare ADRs. Pediatric considerations <ul style="list-style-type: none"> Recruitment challenges may be exacerbated when dealing with children, since the potential pool of patients is already smaller. A prospective observational study may be required if it is not possible to retrieve pediatric-specific information from existing datasets. 	<ul style="list-style-type: none"> A prospective observational study to compare the safety and efficacy of daily vs. intermittent glucocorticoid therapy in boys with Duchenne muscular dystrophy (aged 3–15 years). After age 7, boys on the intermittent regimen declined faster; however, a larger proportion of patients on the daily regimen suffered moderate to severe side-effects. (Ricotti et al., 2013)

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Randomized Controlled Trials (RCTs)	Study Type	Advantages, Disadvantages, Pediatric Considerations	Pediatric Example
	<p>RCT</p> <ul style="list-style-type: none"> • A clinical trial involving randomization and control groups. 	<p>Advantages</p> <ul style="list-style-type: none"> • Compared with observational studies, evidence is more likely to be of high quality and free from other sources of bias. • RCTs provide the strongest evidence for causal relations. <p>Disadvantages</p> <ul style="list-style-type: none"> • May require the recruitment of a large sample of participants, which could be difficult, especially if treatment is available outside the trial. • For rare ADRs, may be difficult even for large multi-centre RCTs to detect differences in adverse events between groups. • Expensive and time-consuming. <p>Pediatric considerations</p> <ul style="list-style-type: none"> • Examples of large-scale pediatric post-marketing RCTs performed solely to examine a safety concern are uncommon. • Post-marketing RCTs for children are more often used to investigate a new dose, pediatric formulation, age group, etc., that has not been previously authorized; these trials are focused on efficacy, but generally include a safety component. 	<ul style="list-style-type: none"> • An unblinded, multi-centre RCT to examine the long-term safety and efficacy of etanercept (a biologic) alone or in combination with methotrexate (a common anti-rheumatic drug) in children with juvenile idiopathic arthritis. • Adverse event rates were similar across all treatment groups and confirmed the findings of previous studies. • The safety profile of the various treatment protocols was considered acceptable. • Effectiveness was similar across treatment arms and improvement was maintained for 3 years. <p style="text-align: right;">(Giannini et al., 2009)</p>

Data Source: Strom (2005b); WHO (2007); IOM (2012a); EMA (2013f)

6.5 ADDRESSING CHALLENGES IN MONITORING AND STUDYING DRUG SAFETY IN CHILDREN

Pharmacovigilance is a fundamentally challenging field; regardless of the population being monitored or studied, rare ADRs can sometimes take several decades to discover (Strom, 2005a). For example, pemoline, a mild central nervous system stimulant that was approved in 1975 for attention deficit hyperactivity disorder (ADHD), was not recognized as a possible causative agent of acute liver failure until the mid-1990s. Finally, after a 25-year period during which children taking pemoline were unknowingly at risk for fatal ADRs, the drug was withdrawn in 1999 and 2005 from the Canadian and United States markets, respectively (Etwel *et al.*, 2008). For a number of reasons, it is even more challenging to generate post-marketing safety data in children than it is in adults. Some of the principal challenges are introduced below and discussed in detail in Table 6.2.

- *Lack of pre-marketing data to support proactive post-marketing surveillance activities:* It is difficult to set up proactive monitoring initiatives for drugs that are prescribed off-label or unlicensed in children, since their pediatric usage may not be widely known. In addition, if pre-marketing studies have not been completed in children, it may be challenging to predict the populations (e.g., age group, co-morbidity) in which the ADR may be most prevalent.
- *Lack of correlation between adult and pediatric safety profiles:* The nature, seriousness, or frequency of an ADR may differ between children and adults taking the same drug. For example, children experience serum sickness-like reactions to the antibiotic cefaclor more often than adults (Stricker & Tijssen, 1992; Vial *et al.*, 1992). In fact, the safety profile of a drug in adults is a poor predictor of its safety profile in children.
- *Fewer children than adults:* The rarity of some ADRs makes their detection difficult, and this problem is exacerbated in children because the pool of potential users for a given drug is small. Furthermore, if an ADR occurs only in a specific age group, the frequency will be even lower.
- *Changing susceptibility to ADRs throughout a patient's lifetime and ADRs with long latency:* In some cases, a particular stage of growth or development may be highly associated with a specific ADR, and in others, an ADR may not manifest until a patient has undergone long-term treatment throughout several stages of development. An additional situation involves ADRs with a long latency period (i.e., those that manifest long after exposure to the drug). These scenarios are difficult to detect without surveillance activities (e.g., active surveillance undertaken by patient registries) and studies that include children of different age groups that are followed over time. Box 6.4 reviews a study that examined long-term outcomes following treatment of children with stimulants for ADHD, which emphasizes the importance of longitudinal analyses.

- *Safety databases that are not conducive to retrieving pediatric-specific data:* Even if prospective monitoring and surveillance initiatives are in place, they may not be helpful for studying pediatric drugs unless they allow the collection and easy retrieval of data such as the age of the child, their diet and nutrition, any concurrent medications, the illness for which the drug was prescribed, and other contextual information.
- *Reluctance to report adverse events, particularly if they have resulted from off-label prescription:* Physicians may be reluctant to report adverse events that arise after they prescribe drugs off-label because of fear of liability.

While some of the challenges are unique to children, others apply more broadly but are magnified in children. Some potential solutions to these challenges are proposed in Table 6.2. Although specific solutions are suggested for each challenge, progress in one area will certainly benefit another (e.g., simplified reporting forms for physicians could lead to higher reporting rates, more complete databases, and ultimately, to enhanced detection of ADRs).

As mentioned, ADRs that manifest after long-term treatment or well after drug exposure are particularly relevant to children. Serious, life-threatening ADRs often happen quickly, sometimes even immediately following drug administration. A classic example is immediate allergic reactions to betalactam antibiotics such as penicillins and cephalosporins (Atanaskovic-Markovic *et al.*, 2005; Novembre *et al.*, 2009). Other ADRs can take days or even years to manifest and are especially important for children if they affect physical or psychological development. ADRs related to central nervous system effects of certain medications are a pediatric concern. For example, antihistamines for the treatment of allergies can be sedating in school-aged children, which can impair their ability to learn (Vuurman *et al.*, 1993; Ng *et al.*, 2004). Antiepileptic drugs can have multiple cognitive effects, including impairment of memory, attention, and language function. Thus, individuals who take these drugs during childhood may deal with long-term deficits in skills such as reading and verbal communication (Ijff & Aldenkamp, 2013).

Stimulants for the treatment of ADHD have also generated concerns (discussed in Box 6.4). Furthermore, antipsychotics are used in children to treat aggressive behaviour associated with ADHD, as well as other behavioural disorders, mood disorders, and psychosis. Data from pediatric trials indicate that antipsychotics may cause metabolic and neurological ADRs, such as weight gain, elevated cholesterol, and abnormal movement disorders (Pringsheim *et al.*, 2011a). This is of particular concern as antipsychotic prescriptions in Canadian children increased significantly more than prescriptions for stimulants from 2005 to 2009 (Pringsheim *et al.*, 2011b).

In September 2013, the American Psychiatric Association released a set of recommendations to guide use of antipsychotics, indicating that physicians and patients should question their routine use as first-line interventions for children, given their serious potential harms (APA, 2013). Several new initiatives in British Columbia, including the Provincial Mental Health Metabolic Program at British Columbia Children's Hospital and the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics, have been created to help parents and doctors manage and monitor the side-effects of antipsychotic medications (Di Pietro & Illes, 2013).

Box 6.4

Health Outcomes Following Use of Stimulant Medications in Children with Attention Deficit Hyperactivity Disorder (ADHD)

A recent Canadian study (Currie *et al.*, 2013) took advantage of the introduction of a mandatory prescription drug insurance law in Quebec in 1997. As a result of the law's expansion of drug insurance coverage, the use of stimulant medications in children with ADHD increased in Quebec relative to the rest of Canada, and the authors investigated whether health outcomes for children with ADHD improved as a result. The study used data from the National Longitudinal Survey of Children and Youth (NLSCY), which began in 1994. Shorter-term outcomes (e.g., behavioural, social, educational, and emotional) were measured in younger children. Older children were followed for up to 11 years after the policy change (until 2008), and the authors labelled the measurements at this time point as *long-term outcomes*. The study found little evidence of improvement in the performance and emotional state of children with ADHD following increased use of stimulants. In fact, in the short term, increased medication use was associated with increased unhappiness, deterioration in relationships with parents, and worse educational outcomes. In the long term, boys using stimulants were more likely to drop out of school and girls were more likely to be diagnosed with a mental or emotional disorder (Currie *et al.*, 2013).

It is not entirely clear from this study whether outcomes in the older children were due to extended treatment with stimulants, a long latency period, or simply use of these drugs at older ages. Nonetheless, these data demonstrate the need to study not only medications that elicit immediate and severe ADRs, but also those that have the potential to affect the emotional development of children.

Table 6.2

Monitoring and Studying Safety Post-Marketing in the Pediatric Population

Challenge	Potential Solution
<p>Attempting to use proactive approaches without adequate pre-marketing data</p> <ul style="list-style-type: none"> Active surveillance initiatives may naturally follow pre-marketing clinical trials. However, if drugs are being prescribed off-label or without a licence, it may not be widely known that children are even receiving them, and hence it may be difficult to set up proactive monitoring studies. In addition, if a safety concern arises, data from pre-marketing trials will not be available as an immediate resource and a starting point for a safety investigation. 	<p>Increase the number and appropriateness of pre-marketing studies in children to inform active surveillance initiatives</p> <ul style="list-style-type: none"> To encourage a focused, proactive approach to identifying ADRs in children, standardized age-specific pharmacology, safety, and efficacy data for particular formulations and delivery routes would be ideal. Drugs that are flagged as potentially problematic during clinical trials (e.g., those approved to treat chronic pediatric conditions) could then be monitored using long-term follow-up registries or cohort studies.
<p>Predicting the likelihood of an ADR in children when only adult safety data exist</p> <ul style="list-style-type: none"> The safety profile of a drug in adults poorly predicts the safety profile in various groups of children. Large-scale, prospective safety studies for a drug may be limited to adults, but these data do not necessarily predict the situation in children. 	<p>Increase the number of pediatric-focused safety studies and analyses</p> <ul style="list-style-type: none"> For an older drug that has been on the market for decades, retrospective analysis of case reports describing ADRs in children may be sufficient for regulatory changes, particularly if the ADR is life-threatening. Newer pediatric drugs present an opportunity for prospective studies or active surveillance initiatives, which can generate data to study the risk of ADRs over time and signal ADRs expeditiously, speeding regulatory action and preventing further ADRs. For both older and newer drugs, supporting studies of ADR mechanisms are also important.
<p>Detecting ADRs that are particularly rare</p> <ul style="list-style-type: none"> Severe ADRs are generally uncommon; if a certain ADR occurs only in a distinct age group of the pediatric population (e.g., due to physiological differences), it will be even rarer and therefore more difficult to detect. 	<p>Better analysis techniques to detect signals for rare ADRs earlier</p> <ul style="list-style-type: none"> Following the first signal (e.g., identified through adverse event reports submitted to regulatory agencies or published literature), potential causal associations between a drug and an adverse event should be investigated; this can be accomplished by applying causality algorithms to the existing data and by launching controlled observational or mechanistic studies to further investigate the association suggested.

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Challenge	Potential Solution
<p>Improving overall detection of ADRs, especially those that are late-onset</p> <ul style="list-style-type: none"> Spontaneous reporting may be less suitable for pediatrics, given the small patient population and thus the low number of possible ADRs, and the fact that infants and children cannot recognize or verbalize their symptoms, leading to under-reporting of adverse events in children. Susceptibility to the side-effects of a drug may not occur until well after a child has begun using it (e.g., if the drug is started during infancy for a chronic condition but the ADR does not become apparent until later in development); for chronic diseases, the total duration of treatment is longer if it is started in childhood, which may increase the risk of an ADR (see Box 6.4). 	<p>More active surveillance initiatives</p> <ul style="list-style-type: none"> Active surveillance systems for detecting ADRs have multiple advantages over passive surveillance. They can generate complete, informative data sets; they can be tailored to the drug (e.g., long-term studies if necessary), the age group (e.g., physiological monitoring for infants who cannot yet verbalize symptoms), and the expected side-effects (e.g., careful attention to liver function). Databases and patient registries set up to collect standardized longitudinal data, even if they are not for the sole purpose of monitoring ADRs, are vital for conducting long-term controlled epidemiological studies (e.g., the Canadian Cystic Fibrosis Registry, or the National Longitudinal Survey of Children and Youth — see Box 6.4); unique patient identifiers used in a system of multiple databases are extremely beneficial, since they allow information stored in separate databases to be linked (e.g., the Saskatchewan health services databases — see Box 6.5).
<p>Extracting pediatric-specific data from drug safety databases</p> <ul style="list-style-type: none"> Databases that collect information on ADRs may be poorly structured, making it difficult to find and interpret information; therefore, it may be impossible to retrieve data on certain age groups. 	<p>Databases with better pediatric coding</p> <ul style="list-style-type: none"> Databases should record and allow for retrieval of standardized age-specific data, other contextual information (e.g., concurrent medications), and parameters such as treatment indication (i.e., what the drug was being prescribed for) to monitor the effects of off-label use; the benefit of recording treatment indication in drug management databases has been shown by the MOXXI (Medical Office for the XXI century) electronic prescribing system in Quebec.
<p>Experiencing reluctance to report adverse events</p> <ul style="list-style-type: none"> Physicians may be reluctant to fill out adverse event reports, because they have heavy workloads and view this task as labour-intensive. Also, they may be unsure of the value of this exercise because of a lack of feedback on how the information is used. When physicians prescribe drugs off-label to pediatric patients, they may be hesitant to report adverse events that result from these practices because of fear of liability. 	<p>Encouraging and simplifying reporting</p> <ul style="list-style-type: none"> Programs designed to enhance adverse event reporting, such as the CPSP ADR initiative, can increase the reporting rate among physicians. Physicians have indicated that more education on ADRs (e.g., tips and reminders), meaningful feedback about their reports (e.g., were reports of similar adverse events received?), and a simplified questionnaire made adverse event reporting more accessible and meaningful and thus increased the likelihood of their filing a report. Manufacturers and regulators should encourage reporting of all suspected ADRs, even if they result from off-label or unlicensed use; reporters should be reassured that their personal data will be protected.

Data Source: EMA (2007); Etwel *et al.* (2008); Eguale *et al.* (2010); Vlahovic-Palceviski and Mentzer (2011); Zimmerman *et al.* (2011); Eguale *et al.* (2012); Sysak (2012); Vogel and Sysak (2012); Kuehn (2013); Niesters *et al.* (2013)

Potential solutions for improving pediatric pharmacovigilance can be envisioned along a timeline that begins in the pre-marketing phase. By conducting clinical trials in children instead of relying on off-label use, more common pediatric ADRs can be identified before a drug enters the market. Although ideal, this kind of study and reporting are rarely undertaken. Recognizing that clinical trials are not typically powered to measure overall safety and usually measure only a few factors, if ADRs detected in pre-marketing trials are sufficiently frequent and severe, this early knowledge may lead to a pediatric contraindication for a drug. Less serious concerns can be used to justify post-marketing safety studies. Once a drug reaches the market, even if no pediatric safety concerns were flagged in pre-marketing trials, targeted active surveillance is the preferred method for safety monitoring. Passive surveillance suffers from numerous issues (see Section 6.3), including high levels of under-reporting (Hazell & Shakir, 2006). However, because active surveillance may not be feasible for every drug, especially in a large jurisdiction like Canada, programs to encourage reporting and better techniques for detecting and analyzing safety signals would be beneficial.

The success of these post-marketing safety initiatives depends on the quality of the databases that are used to collect information. Pediatric coding in databases (e.g., information such as the age of the patient and the drug formulation) is often insufficient enough to allow pediatric ADRs to be analyzed. The Canada Vigilance Adverse Reaction Online Database maintained by Health Canada has been described as poorly structured and difficult to interpret. A single record often displays multiple medications and multiple adverse events, and thus suspected ADRs are difficult to identify (Sysak, 2012; Vogel & Sysak, 2012). A system of standardized, linkable databases across the country, or even across multiple countries, would be highly beneficial for pediatric surveillance of ADRs, since it could increase sample sizes for rare ADRs to levels that allow robust analyses (Neubert *et al.*, 2008). Sufficient pediatric data would also facilitate comparisons between adults and children to see if there is a higher incidence of ADRs in children that warrants a different approach or heightened awareness by children, parents, and providers.

The Saskatchewan health services databases (described in Box 6.5) are an exemplary group of efficient and user-friendly Canadian databases that provide a useful model for this type of linked system.

Box 6.5**Saskatchewan Health Services Databases**

Upon registering with Saskatchewan Health, residents are eligible for coverage under a prescription drug plan that covers all products listed in the Saskatchewan formulary. Each resident is assigned a unique Health Services Number (HSN), used when information is entered into any database, allowing information stored in different databases to be linked. Major databases include the population registry, prescription drug database, hospital services database, and physician services database. Examples of fields in the prescription drug database are patient age, drug strength and dosage form, and drug active ingredient number (assigned by Health Canada), all of which are helpful for pediatric analyses. Linkages between databases using the HSN allow data to be merged and sorted based on age, sex, diagnosis, and many other parameters. Although not designed for research purposes, the Saskatchewan health services databases have been used for numerous studies, including long-term studies of drug exposure and health outcomes such as long-term adverse effects (Downey *et al.*, 2005). Long-term studies are particularly beneficial for children's health, to identify any delayed effects on growth or development (see Box 6.4). From a national perspective, a limitation of the Saskatchewan system for drug-related data is that it is based on public plan drug coverage, which varies for children across provinces (Ungar & Witkos, 2005). Therefore, if a similar system were implemented across Canada, data for certain pediatric populations would be captured in some provinces but not others.

6.6 TOWARDS AN INTEGRATED APPROACH TO POST-MARKETING SAFETY IN CANADA**6.6.1 Integration of Data from Various Passive and Active Methods**

There are numerous methods to consider when gathering and analyzing information in the post-marketing setting. While the usefulness of each method may depend on the specific post-marketing safety issue, investigation of a given drug will likely involve several methods, progressing from processes that are faster and less expensive to those that require more time and resources (Strom, 2005b). Safety signals may first be identified from passive or active surveillance, cases reported in the literature, or a targeted review of adverse event databases (e.g., the Canada Vigilance Adverse Reaction Online Database or the FDA Adverse Event Reporting System). Once a signal is identified, adverse event cases may first be analyzed individually using causality algorithms and subsequently assessed in a controlled retrospective study to confirm a causal link between a drug and an adverse event and to estimate the probability that the

ADR will occur. Active surveillance initiatives would make it easier to perform analyses from more complete data sets. Databases that follow patients over time or studies that include children of different ages are essential for detecting ADRs that occur after long-term treatment or following a long latency period. Retrospective observational studies offer several advantages for pediatrics over prospective studies, including faster results, greater suitability for smaller populations, and greater sensitivity for rare events (such as ADRs that arise from drugs prescribed for rare pediatric diseases). Any prospective studies, whether they are observational studies or RCTs, may face difficulties recruiting enough children to detect rare ADRs in a timely fashion. As discussed earlier, although RCTs are generally considered to produce evidence of the highest quality, they may not be practically feasible, especially if evidence is required quickly. Furthermore, the rigorous evidence provided by an RCT may not be necessary to make a regulatory decision about a pediatric drug, particularly if children are at risk for a life-threatening ADR. However, RCTs are usually needed if manufacturers or researchers are seeking efficacy data for a new indication (e.g., a new formulation or use of the drug in an unapproved age group).

6.6.2 Lifecycle Approach

Health Canada has recognized the need for a *lifecycle approach* to health product vigilance that would involve continually assessing the risks, benefits, and recommended uses of a medicine post-marketing and over the long term. A major component of this approach are risk management plans (RMPs), particularly for products that are poorly characterized or those that are known to have greater risks. RMPs include a summary of the known safety information for the product, plans to investigate known or potential safety concerns, and plans to minimize any identified or potential safety risk. Manufacturers currently submit RMPs to Health Canada on a voluntary basis (HC, 2012g).

One key to implementing a lifecycle strategy is to improve the integration of pre- and post-marketing activities and communication between the regulator (Health Canada), public health agencies, and industry stakeholders. Public health practitioners are typically involved in the post-marketing phase, studying drug safety after authorization decisions have been made by the regulator. However, public health groups may be able to play a role in the pre-marketing period by helping to identify potential safety issues and specific populations in which they may occur. It may be practical for Health Canada to work with the Public Health Agency of Canada (PHAC) — the national agency with a population-level perspective on infectious diseases, chronic conditions, injuries, and child health. PHAC may help to inform pre- and post-marketing decisions and include a public health perspective in market authorization discussions with industry manufacturers. In order for a lifecycle approach to be beneficial

for children, it will be important to ensure that they are not excluded at any stage of the drug research process and that their needs are met by adapting standard adult practices.

6.6.3 Post-Marketing Regulatory Lessons for Canada

Previous sections of Chapter 6 have mentioned some of the differences among various jurisdictions in regulatory requirements for generating and analyzing post-marketing safety data. Table 6.3 summarizes these regulations.

Table 6.3
Canadian and International Regulatory Requirements for Adverse Event Reporting and Post-Marketing Studies

Regulatory Agency	Requirements for Adverse Event Reporting	Authority to Mandate Post-Marketing Studies
<p>Health Canada</p>	<ul style="list-style-type: none"> • Every MAH* is required to report any suspected ADR to Health Canada’s Marketed Health Products Directorate. • Domestic ADR reports (i.e., those that occur in Canada as a result of a product that is marketed in Canada) must be submitted for serious ADRs and unusual failures in efficacy.** • Foreign ADR reports (i.e., those that occur outside Canada as a result of a product that is marketed in Canada) must be submitted for serious <i>unexpected</i> ADRs (reactions inconsistent with those described in the Canadian product label or monograph). 	<ul style="list-style-type: none"> • Health Canada currently has no authority to require new efficacy, therapeutic effectiveness, or safety data from MAHs at the time of market approval. • Health Canada’s Clinical Trials Database does not include post-marketing trials.
<p>FDA</p>	<ul style="list-style-type: none"> • Reporting of adverse events is required for manufacturers but voluntary for health care professionals and consumers. • Reports are entered into the FAERS and VAERS databases and may be analyzed further using the Sentinel Initiative (see Section 6.3.4). 	<ul style="list-style-type: none"> • Before 2007, the FDA required post-marketing studies in a limited number of situations, one of which involved deferred pediatric studies (see discussion of PREA in Section 2.3.1). • In 2007, the FDA was granted authorization to require post-marketing studies at the time of approval or after approval if there is concern of serious risk. • Research may be conducted to assess a known risk, to assess signals of risk, or to identify an unexpected risk. • Safety reviews overseen by the Pediatric Advisory Committee are required within 18 months to continually assess potential safety concerns arising from pediatric drug labelling changes.

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Regulatory Agency	Requirements for Adverse Event Reporting	Authority to Mandate Post-Marketing Studies
EMA	<ul style="list-style-type: none"> • New legislation for pharmacovigilance was implemented in July 2012. • MAHs are legally obligated to track and report all suspected ADRs and, in some member states, reporting is mandatory for health care professionals and encouraged (not mandatory) for consumers. • The EMA does not accept adverse event reports directly; they are reported to the competent authority for each member state. • Competent authorities (i.e., regulatory bodies with legal authority) are required to have systems in place for collecting and recording adverse event reports, which they receive from MAHs, health care professionals, or consumers; the authorities share this information with the EMA so that it can be amalgamated in the single E.U. database (EudraVigilance) and analyzed. 	<ul style="list-style-type: none"> • E.U. competent authorities require Risk Management Plans (methods to prevent and minimize ADRs) and may request post-authorization safety study(ies) or post-authorization efficacy study(ies). • Similar to the FDA, a post-market authorization safety or efficacy study can be requested in the pre-authorization phase as a condition of market authorization or during the post-authorization phase when there are concerns about the risks of an authorized medicinal product. • Although manufacturers are not allowed to promote off-label use, the EMA monitors this use closely in children using Risk Management Plans. It further states that the age or age group of a drug recipient should be submitted in an adverse event report made to EudraVigilance, so that safety signals specific to subgroups can be identified.

Data Source: HC (2002); FDA (2005b); EMA (2007); FDA (2011); HC (2011a, 2011b); EMA (2012c, 2012d); FDA (2012a); EMA (2013f); HC (2013b)

* *Market Authorization Holders* (MAHs) are also referred to as sponsors or manufacturers. In Canada, an "MAH is the legal entity that holds the Notice of Compliance, the Drug Identification Number (DIN), the medical device licence number, the product licence number, or that has received approval to initiate clinical trials in Canada" (HC, 2005b).

** An *unusual failure* in efficacy refers to the worsening of a patient's condition due to the failure of a drug to produce its expected intended effect. Examples would be a "previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription" or "a life-threatening infection where the failure in efficacy seems to be due to the development of a newly resistant strain of bacterium previously regarded as susceptible" (HC, 2011a).

Health Canada has less authority than regulatory agencies in other jurisdictions, and the need to improve its current pharmacovigilance system has been recognized. A 2013 report by the Standing Senate Committee on Social Affairs, Science and Technology found that post-marketing studies are necessary to accurately measure real-world safety and efficacy of drugs and that the adverse event reports collected by Health Canada are insufficient (Senate, 2013). The Senate Committee therefore recommended that Health Canada be given the authority to require post-marketing studies and made several other recommendations for improving post-marketing monitoring in Canada, including a large-scale

analysis of the performance, organization, and budgetary needs of the Drug Safety and Effectiveness Network (DSEN) (see Box 6.3). The Senate Committee further stated that improved post-marketing studies are especially important for vulnerable populations such as children. If a drug has not been thoroughly studied in a given population during pre-marketing trials, then post-marketing studies provide an opportunity to identify subgroups who respond well to a drug and those at risk for severe ADRs. To address this issue, the Senate Committee recommended implementing a post-marketing strategy that prioritizes the study of new drugs in relevant sub-groups of the population (Senate, 2013).

6.7 CHAPTER SUMMARY

While safety trials are conducted in the pre-marketing phase, Phase I, II, and III clinical trials are usually too small to detect rare ADRs and more common ADRs in sub-populations, including children. Furthermore, the lack of pre-marketing trials in children and consequent off-label use effectively means that safety is often monitored only in post-marketing real-world settings. However, even post-marketing surveillance may miss ADRs in children because of several factors: low levels of voluntary reporting, especially for off-label use; children's — especially younger children's — inability to identify and express symptoms; and databases that are not conducive to retrieving pediatric-specific information and not set up to collect longitudinal data for monitoring of ADRs that appear long after use or only after use for extended periods.

These gaps in identifying ADRs and ensuring the safety of children also highlight issues with the post-marketing surveillance and clinical trial system in Canada. Surveillance is mainly passive, with few initiatives for stimulated reporting or active surveillance; no incentives exist for manufacturers to conduct further studies in specific patient groups after marketing. Other jurisdictions have adopted guidance or regulations to improve surveillance and continued post-marketing clinical research. The establishment of the DSEN in Canada holds promise for targeted post-marketing research. DSEN has already launched funding opportunities that encourage pediatric research, and DSEN teams have undertaken two large projects that focus on drug safety in children (Dormuth *et al.*, 2013; Filion *et al.*, 2014).

The development of safer and more effective medicines for children would be facilitated by active surveillance initiatives that record comprehensive information in user-friendly, linkable databases or registries with better pediatric coding; this would make it easier to conduct post-marketing observational studies that can identify causal associations between drugs and adverse events. For children, it is particularly important to ensure that ADRs that may affect physical or psychological development are investigated using long-term follow-up studies; these studies would be facilitated by databases or registries that collect longitudinal data.

The most widely used algorithms for judging the likelihood of a causal link in individual adverse event cases are not always valid or reliable for ADRs in children. Researchers are working on creating causality assessment tools that are specific to pediatrics. To advance drug surveillance, novel approaches are being developed, such as the construction of computational networks that integrate multiple sources of information (e.g., from adverse event databases, developmental pharmacokinetics, and genetics) to predict ADRs before they occur. Active surveillance is also being used to evaluate ADR mechanisms, by coupling it with screening to discover genetic variants that predispose individuals to ADRs (Carleton, 2010). A combination of active surveillance for faster identification of ADR signals, pediatric-focused algorithms, observational studies for verifying and quantifying risk, and the development of tools to predict the likelihood of an ADR based on genetics and drug–drug interactions will help ensure the safety of medicines for children.

7

Supporting Safe and Effective Therapeutic Products for Children

- 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?
- Future Research Questions
- Final Panel Reflections

7 Supporting Safe and Effective Therapeutic Products for Children

The evidence is clear on the need for pediatric medicines. Each year, about half of Canada's seven million children use at least one prescription medication. Much of this prescribing is off-label, outside of official approval, a practice that may introduce unnecessary risk of harm to children who need medicine. The current regulatory incentive for manufacturers to submit study results on the use of medicines in children during drug approval has had limited success. To ensure that therapies for Canadian children are effective, drugs used in children need to be tested appropriately in children, and the regulator may need levers to require the submission of these study results.

Within this context, the Panel was tasked with answering the following charge:

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?

In developing its assessment, the Panel reviewed the evidence from a range of sources, and this knowledge is presented in Chapters 2 through 6. This chapter summarizes the state of the evidence, identifies opportunities for future policy and research, and provides the Panel's conclusions and final reflections. It is organized according to the sub-questions of the charge.

7.1 HOW DOES HUMAN DEVELOPMENT FROM INFANCY TO YOUTH ALTER CLINICAL PHARMACOLOGY AND THEREFORE INFORM PEDIATRIC DRUG INVESTIGATIONS?

Children are different from adults. As children progress from infancy through to adolescence, a number of significant developmental changes occur. These changes impact how their bodies deal with medications (pharmacokinetics) and how medications, in turn, affect their bodies (pharmacodynamics). These factors cannot be accommodated by simply adjusting an adult dose. The physiological systems that process drugs change over time, with the most dramatic age-related physiological changes taking place during the first year of life. A newborn will respond to a drug differently than an adolescent will, and this variability in response is not a linear progression but rather a dynamic process dependent on age, weight, the drugs and conditions involved, and individual and environmental factors. It is therefore important to take into account different age and weight ranges and involve children at all stages of development in clinical pharmacological research.

Children are also different from one another. Genetic variations, interpreted in the context of growth and maturation, can impact how children respond to drugs. Pharmacogenomics and pharmacogenetics hold promise for further explaining and predicting differential responses between children, including adverse drug reactions (ADRs). In assessing the state of the evidence, the Panel observed that there is more accumulated evidence on pharmacokinetics than on pharmacodynamics. Furthermore, there is a general lack of pharmacokinetic, pharmacodynamic, and pharmacogenomic evidence related to children, particularly pre-term newborns, newborns, and young infants. In pharmacogenomic and personalized medicines research, this gap is even more pronounced, given that these are relatively new fields, and their clinical implications for drug therapy in children remain largely unexplored.

These developmental and genetic differences need to be taken into account to ensure safety, efficacy, and optimal drug treatment from birth through adolescence. Individual studies will continue to contribute incrementally to the body of knowledge in pharmacokinetics, pharmacodynamics, and pharmacogenomics. While all research in these fields is useful, large-scale, coordinated, and concerted efforts are needed to develop better treatment options and effective new medications for children.

Evolving knowledge of research methods and clinical pharmacology can inform these investigations. For example, new methods for collecting biological specimens (e.g., scavenged blood sampling) and analyzing small samples can help to minimize distress in children and increase study efficiency. Information about interactions of human development and individual traits on pharmacokinetic and pharmacodynamic processes can inform the design of pediatric drug investigations. Modelling and simulation (M&S) techniques harness information to predict drug exposure and response in children and can therefore help with study planning and analysis.

In addition to the effects of age and genetics, children may respond differently to drugs depending on their disease state, environment, and social and demographic characteristics. Hence, pediatric medicines research needs to clearly establish which populations are safely treated with different drugs. Within the pediatric population, a comprehensive approach would include those from all ages, a range of conditions, and varying social and economic circumstances and environments. Involving diverse participants in future clinical pharmacological research can enhance the applicability of the results. Knowledge of how human development and individual and environmental characteristics alter drug response in children would inform more specific therapies, with potentially unique safety and efficacy profiles.

Those who are responsible for formulating and administering medications need to take into account children's unique characteristics, both in research and real-world applications. The availability of suitable pediatric forms and formulations is critical for facilitating accurate and easily adjusted dosage of a medication, optimizing drug bioavailability, and ensuring the efficacy and safety of treatment for children. A range of forms should be available to ensure that the delivery of a medication is accurate and the dosage can be easily adjusted to account for changing requirements related to development. Formulations that appeal to children's preferences for appearance, taste, smell, and texture help ensure adherence to medication regimens. Ultimately, the accuracy of the dose, the effect of excipients, the palatability of the drug, the drug packaging, and the selection of an appropriate delivery route and device (e.g., inhaler or syringe) are all particularly important considerations for children. A number of novel delivery devices have recently been developed that target routes of delivery appropriate for children. Without appropriate forms and formulations there is an increased risk of error, exposure to unsafe medication components, and general lack of efficacy. For these reasons, pediatric-specific forms and formulations hold numerous advantages over relying on adult forms and formulations.

Work is underway internationally to develop clear and transferable evidence related to forms and formulations, including appropriate excipients, palatability, delivery devices, dispensing, extemporaneous formulations, and age-appropriate formulations. Many of these initiatives are unique partnerships among academia, clinical settings, industry, and regulators. Collaborating across sectors and sharing information are important for improving efficacy and safety of medications for children. There are many opportunities for Canada to join these international efforts to ensure that ultimately children receive timely, accurate, and properly administered doses of medications.

Moving Forward — An Opportunity to Inform Pediatric-Specific Medicines

- The evidence base for pediatric clinical pharmacology could be strengthened with regulatory authority to require complete submission of all data from studies; this is an authority that Health Canada does not currently possess.
- The Panel identified an opportunity for Canada to develop a source of up-to-date pediatric-specific evidence to inform real-world use of medicines. A comprehensive prescribing resource endorsed across Canada would close an important information gap in child health care. To support informed prescribing, this resource would provide clear dosing guidelines for all age groups and for all indications for which evidence-based data are available. This type of formulary could draw on scientific studies conducted for regulatory approval as well as other sources of evidence, such as published peer-reviewed studies. The resource would be peer reviewed, or otherwise recognizably validated, updated regularly, and available to all prescribers.

- A coordinated agenda among sectors is needed to drive large-scale concerted efforts related to pediatric clinical pharmacology. Such efforts include improved education and training opportunities in this area, increased pharmacokinetic and pharmacodynamic research in children, and facilitating multi-centre studies and research networks that build a diverse set of evidence and maximize the research strengths that exist across jurisdictions. Such collaboration could encourage documenting (e.g., pharmacokinetics databank), sharing, and synthesizing available knowledge to maximize the use of information and reduce duplication and burden in future research. Networks can also provide a channel to effectively translate knowledge to educational and clinical settings, to support prescribing decisions.
- Pharmacogenomic data can improve the quality of care for children by leading to individualized clinical therapies that maximize effectiveness and minimize toxicity. Genetic testing should prove useful in designing effective therapeutic regimens in children with a number of conditions in which there is known genetic variation and high clinical relevance. Because the technologies for obtaining and analyzing genetic information are constantly evolving, there will be new opportunities for research and personalized care.
- While past drug development for children has focused primarily on liquids, the future of drug development involves dissolvable tablets, minitables, drug–device combinations, and other novel forms of drug delivery that will allow for more accurate and acceptable administration of drugs as well as dosing adjustment and flexibility.
- The best scenario for treatment of children involves commercially available age-appropriate forms and formulations with known bioavailability. In the absence of such forms and formulations, guidance on appropriate modifications would improve efficacy and safety of drugs. Specific, detailed, standardized, and evidence-based recipes for preparing safe extemporaneous formulations should be provided.

7.2 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?

As with adults, the best practice for studying the efficacy of medicines for children is a randomized controlled trial (RCT). However, before planning such a clinical trial, a rigorous synthesis of existing evidence is an essential starting point. Analysis of prior data (from animals, adults, and children) may suggest that further clinical studies can be reduced in scope or avoided altogether if extrapolation is possible; if they are deemed necessary, this analysis will also likely reveal information that will be helpful for planning a new study.

RCTs conducted at multiple study sites or centres are beneficial to increase statistical power and study validity if only small numbers of children are eligible or available, which is often the case with rare diseases. Multi-centre studies undertaken by large-scale, collaborative research initiatives such as the Children's Oncology Group (COG) represent the ideal solution to the issue of small target populations. These initiatives facilitate multi-centre RCTs that use standardized protocols to research different treatments for the same condition, allowing for comparisons among thousands of patients even for rare diseases. Standardized pediatric-specific forms and formulations evaluated with pediatric-specific outcome measures would help to produce relevant evidence to the highest standard. In addition, international organizations are working to standardize age groups and pediatric outcomes. RCTs with children in Canada would benefit from these efforts to maximize the value of information across sites.

The Best Practices for Health Research Involving Children and Adolescents: Genetic, Pharmaceutical and Longitudinal Studies report, an important Canadian reference document, provides ethical guidance in new areas such as genetic research and biobanks; however, concrete standards have not been developed, either in Canada or elsewhere, for some of these emerging areas (CGP & MICYRN, 2012). As well, Canada's nationally enforced policy on research ethics — the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* — was recently updated and acknowledges the value and importance of research in children (Tri-Council, 2010).

There are numerous ways in which RCTs can be modified to enhance their flexibility. Pediatric researchers may benefit from these modified designs to improve the acceptability of trials for patients and their families (e.g., to decrease the amount of time spent on placebo, to ensure that all patients eventually receive the treatment, or to allow trial adaptations based on accumulating data). Such flexible approaches can ensure that children are included in research rather than inappropriately relying on research in adults. Where a modified design is necessary, studies can still be conducted in a rigorous manner. Research can begin by using an alternative design, and, as evidence accumulates, the investigation may proceed to a classic parallel group RCT, particularly if additional resources or infrastructure become available to allow a multi-centre trial.

In contrast to studying the efficacy of medicines, the best practice for studying safety is likely not an RCT. Although common ADRs may be identified during pre-marketing RCTs, detecting rare ADRs often requires post-marketing collection and analysis of safety data. In the post-marketing setting even large multi-centre RCTs may miss rare but serious ADRs. Instead, the study of drug

safety post-marketing involves identifying safety signals from monitoring initiatives. Signal detection is followed by analysis of causality and possible completion of large-scale observational studies to assess incidence and risk. Best practices for these various stages include establishing active surveillance initiatives that record comprehensive information about ADRs in user-friendly databases with pediatric-specific information, developing valid and reliable tools for judging causality in pediatric ADR cases, and using existing information in monitoring databases efficiently and systematically to complete retrospective observational studies.

Different types of ADRs may lend themselves to different study approaches. For example, events that are rare or considerably delayed after a drug is administered may be better suited to a retrospective observational design. However, similar to studying efficacy, establishing safety of medicines for children can involve various methods and may require the flexibility to progress between methods. Investigations that begin with case reports and analysis of surveillance databases may progress to case-control or cohort studies, and if necessary and feasible, to RCTs to estimate incidence and relative risk. Any best practice for study design can be combined with active surveillance methods, and this integrated approach holds promise over solely passive approaches for identifying rare ADRs.

A more dynamic lifecycle approach may provide better integration of pre- and post-marketing safety data. Pre-approval studies in children would support post-approval monitoring by identifying possible ADRs for ongoing surveillance. There is also an opportunity for better linking of data 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.

There are several opportunities for standardizing drug studies, both for safety and efficacy. These include harmonizing ethics reviews among Research Ethics Boards, developing common templates and outcome measures, and using emerging research approaches and data collection methods. These measures can help researchers make best use of often-limited research resources and more readily compare their findings.

To make the process of authorizing medicines more flexible and responsive while maintaining scientific rigour, there are also opportunities for scientists and regulators to define admissible evidence for the drug approval process. These requirements can then be integrated into study design from early in the planning process. Similarly, the regulator can determine the timing of pediatric studies in relation to adult trials, recognizing that timing influences the availability of the medicine. Post-approval safety studies with long-term

follow-up could also be made a condition of drug approval in cases where ADRs are expected to be delayed. Any future efforts in surveillance could also include better monitoring and understanding of off-label use.

Moving Forward — An Opportunity to Encourage Pediatric Research

- Although children are physiologically different from adults, best scientific and ethical practices in research specific to adults are easily transferable to research with children. Canada would benefit from a system that encourages studies in children, recognizing that children need to be protected through research, not from research. Such a system should also encourage the synthesis of available knowledge to maximize the use of information and reduce duplication and burden in future research.
- The Panel identified an opportunity for Canadian regulators to use a wider variety of policy options. Legislative and regulatory measures in the United States and European Union provide some guidance, and Canada can select options that best fit the needs of Canadian children and the capacities of Canadian researchers. These options could be supportive (e.g., funding for research or data protection) but could also involve formal requirements and regulations (e.g., the obligation to submit data on pediatric safety and efficacy). Incentives for research could foster high-quality, limited-cost trials with optimal study designs that are innovative where needed. Trials are commonly conducted in ways that would not meet regulatory standards (e.g., including an insufficient number of children), which limits the relevance of the results for establishing efficacy and safety of a drug. Regulators could support the quality required, while considering appropriate flexibility in setting requirements for evidence in the drug approval process.
- A pan-Canadian research agenda, or pediatric drug development initiative, that engages all stakeholders — patients, families, care providers, researchers, regulators, industry experts, ethicists, and funders — could be useful for advancing pediatric clinical pharmacology in Canada and internationally. Many of the resources required for such an agenda (e.g., technical and clinical expertise, training facilities, research networks, and database infrastructure) are in place, but a unified effort has not been defined. In addition to direct participation in global collaborations, Canada can draw on the experience of other jurisdictions in fostering effective made-in-Canada networks. This experience includes sustainable and ongoing infrastructure that can support individual studies and increase consistency and comparability across studies. Constructing an effective legal framework to harmonize the process of research would also be useful. A shared research effort might improve the results of studies, bringing them to the standards for regulatory approval.

- There is promise in further developing and supporting pan-Canadian networks and collaboration across health care centres and researchers running trials. Encouraging complementary — rather than competing — efforts through multi-centre trials, networks, and use of existing evidence is essential.
- 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 and regulators (e.g., on acceptable evidence), between investigators and clinicians (e.g., on forms and formulations used in studies that must be applied in the real world), and between investigators and patients and their families (e.g., on the outcomes that matter, and benefits and harms of different treatment).

7.3 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?

The Panel concludes that demonstrating safety and efficacy of a medicine in studies involving children as participants is always possible and feasible, both in terms of ethics and methodologically.²⁶ However, there may be circumstances in which drug studies involving children pose research difficulties. For example, in the case of a rare condition, finding enough children may be challenging. In addition, if participation means a child may not receive a new treatment, parents may be unwilling to provide consent for their children's participation. The Panel has identified options to address each of these complexities, many of which require researchers to be flexible in their approach. The Panel underscores that many study designs are possible and appropriate for pediatric research, although they are sometimes poorly understood, particularly adaptive study designs. In the rare cases that it is not possible to study drug efficacy in children using RCTs, observational studies are a possibility, but they are more appropriate for post-marketing safety studies. Despite this lack of understanding, some new approaches hold promise for improving the efficiency of studies with children. For this potential to be realized, pediatric research and regulation need a culture shift.

Involving children in post-marketing safety monitoring and studies is less challenging, since most of the methods used during the post-marketing phase involve surveillance or observational studies, which are less invasive than experimental trials. As a best practice, researchers are encouraged to use active

²⁶ A rare, although notable, exception is counterterrorism measures, in which the ethical issues are considerable barriers to including children as participants. These situations are outside the scope of the Panel's assessment.

surveillance, which facilitates collecting ADR datasets that are better standardized and more complete than those generated by passive or stimulated surveillance. If a jurisdiction has a well-linked database system to track health-related information, data from both cases (people who experience an adverse event) and controls (people who do not experience an adverse event) may be available, which will enable subsequent completion of retrospective observational studies.

Moving Forward — An Opportunity to Promote Flexibility in Research

- The Panel identified an opportunity for regulatory guidance to encourage pediatric research in ways that balance feasibility with the needs of children. Evaluation of best pediatric practices for regulatory drug-development systems in other jurisdictions shows that the timing of studies (i.e., whether pre-marketing studies are required or post-marketing study would be more appropriate) and the availability of the evidence (i.e., recording of and open access to pediatric-specific data in databases concerning health and ADRs) are both important considerations. The regulatory framework could further promote flexibility and an open-minded approach to different research designs.
- There is great potential in adopting a flexible approach when determining study design and analysis techniques. Adaptive and innovative designs make trials involving children more feasible. As knowledge builds, researchers can progress to larger, more robust, and comprehensive study designs.
- An opportunity exists for open dialogue between investigators and Canadian regulators on flexible study designs that are feasible for investigators and acceptable for regulatory approval of drugs for pediatric use. As stated, the Panel's view is that studying medicines in children is almost always methodologically feasible, but it is currently unclear whether regulators will accept the data generated by non-standard approaches for drug approval. If Canadian regulators can provide concrete guidance on situations in which alternative designs may be accepted as evidence, this would encourage the use of these designs by investigators, allowing both parties to gain further experience with these approaches.

7.4 WHAT ARE CANADA'S STRENGTHS TO CONTRIBUTE TO GLOBAL PHARMACOVIGILANCE EFFORTS FOR DRUGS THAT MAY BENEFIT INFANTS, CHILDREN, AND YOUTH?

In the Panel's assessment, pharmacovigilance entails more than monitoring safety and ADRs. It also includes studying efficacy and safety over the entire product lifecycle. There are a range of international best practices and standards for the conduct of clinical trials, research studies, and pharmacovigilance efforts, for which Health Canada could consider creating requirements for researchers.

However, Canada also has existing infrastructure and human capacity with the concerted strength and willingness to generate new knowledge about medicines for children.

Pediatric information in databases could be improved and the linkages between various databases could be strengthened, according to the Panel's assessment of the evidence. Yet even the existing databases represent significant untapped investments that hold valuable information on population health and on drug use in children. These databases represent a Canadian resource — the experience of building and maintaining databases as well as the data contained therein — that could be shared as part of a global pharmacovigilance effort. For example, the Canadian Network for Observational Drug Effect Studies (CNODES) has demonstrated the power of harnessing information from multiple Canadian and international databases to complete large-scale studies on ADRs. In its inaugural study, CNODES used administrative records from seven Canadian provinces and two international databases (from the United Kingdom and United States) (Dormuth *et al.*, 2013). Improved pediatric coding in databases would facilitate use of administrative records for studying ADRs in children. Although not implemented nationally, Canada has some examples of well-organized, linkable database systems for the collection of health care data (e.g., the Saskatchewan health services databases discussed in Chapter 6).

Canada has a proven track record in pediatric research. Researchers at several well-respected Canadian children's hospitals have led high-quality and high-profile international studies (e.g., the Caffeine for Apnea of Prematurity (CAP) study described in Chapter 5). This track record also illustrates the capacity of Canadian researchers and research institutions, many of which work through and with established networks. Some of these arrangements — such as the Maternal Infant Child and Youth Research Network (MICYRN), the Drug Safety and Effectiveness Network (DSEN), and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) — are uniquely Canadian. These networks showcase Canadian leadership and bring together highly skilled investigators working on similar topics. Other network initiatives are supported by Canadian researchers in collaboration with international counterparts, for example, GRiP and StaR Child Health. Collaborations across borders provide formal connections with regulators and researchers abroad — such as through MICYRN's link to the network Enpr-EMA of the EMA Paediatric Committee (PDCO) — and may also signal areas of international leadership that could guide Canada's exploration of policy options on particular issues.

Canada has also introduced new initiatives for monitoring the long-term effects of drugs for treating disorders related to behaviour, mood, and psychosis. This is an important pediatric issue since use of these drugs in children is increasing and they have recognized but understudied long-term effects that may negatively influence physical or psychological development. These new Canadian initiatives (e.g., the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics), are embracing a multidimensional approach that includes parents in monitoring and managing ADRs associated with drugs (Di Pietro & Illes, 2013).

Moving Forward — An Opportunity to Encourage Shared Learning

- The Panel identified the opportunity for strong research infrastructure that can enable the development of scientific knowledge of safety and efficacy of drugs in children. Such infrastructure includes the development of networks, in which Canada has considerable existing capacity. This capacity could be fostered and further developed.
- Canada is a multicultural society with diverse populations and environments. Researchers could capitalize on this diversity, building an understanding of efficacy and safety issues across a range of populations.
- Canadian researchers and organizations demonstrate considerable capacity in clinical trial infrastructure. This capacity is interdisciplinary, drawing on a range of clinical perspectives to produce a complementary suite of skills that are unique to Canada. This infrastructure could be significantly reinforced.

7.5 FUTURE RESEARCH QUESTIONS

In its review of the evidence, the Panel identified some areas of the charge that were challenging to assess and that could serve as areas for future research:

- How can evidence accumulated from individual studies on developmental pharmacokinetics, pharmacodynamics, pharmacogenomics, and appropriate forms and formulations for different age groups and populations be made available and systematically integrated into drug investigations and prescribing practices in clinical settings?
- The results of pediatric studies conducted in Canada and elsewhere are rarely submitted to Health Canada as part of the drug approval process. This has implications for clinical pharmacology, prescribing practices, and accessibility of safe and effective medications. Are there mechanisms to support investigators in submitting results to the Canadian regulator and maximizing the return on investment in research with children?

- A range of approval processes across multiple sites in Canada is a major challenge for conducting robust multi-centre studies. The evidence points to the benefits of improving harmonization and linking approval processes among academic institutions or approval bodies such as Research Ethics Boards. What authority is best placed to provide the mandate and legal protection to support the emerging cooperation in harmonized review processes?
- How can regulators encourage studies of off-label drugs? The most apparent solution is to give Canadian regulators the authority to mandate both pre- and post-marketing studies. Are there any additional incentives that could encourage investigators to study off-label pediatric uses of drugs already approved for use in adults? When there are multiple companies marketing multiple versions of a product, who does the regulator encourage to do the study?
- What mechanisms could encourage a culture shift that promotes openness to engage in research among clinicians, patients, and families?

7.6 FINAL PANEL REFLECTIONS

Scientific studies both inform regulatory decisions and are the basis of the practice of medicine. A lack of scientific evidence for clinical use can expose a patient to unnecessary risk of harm; for some aspects of pediatric medicines, the unknowns are many. For other treatments, there is credible information, but a failure to use that information may result in harm to those in need of care. Building new knowledge involves using scientific methods to produce evidence, but using evidence ethically also requires wisdom. The Panel recognized the contribution of sound evidence and built their assessment on credible and rigorously evaluated facts. As scientists, researchers, and clinicians, each member of the Panel was chosen for his or her knowledge and experience; however, this group of individuals with different disciplinary philosophies and approaches realized a consensus on a set of shared values as a result of reviewing the evidence. The Panel's assessment was guided by those values and principles that are rooted in evidence but also the social responsibility that underpins careful science.

Children Have a Right to Health and Well-Being

Children's right to health includes a right to medicines that are well-studied and approved for use in their age group. Children deserve timely and equitable access to safe and effective treatments and care, including participation in research.

Children Are Different and Diverse

Children differ from adults in their responses to medicines. The difference begins in biology, but also involves developmental and social factors that influence the administration of drugs, the design of research, and the monitoring of and response to safety concerns.

In a country with a diverse and dispersed population like Canada's, factors such as income and geography can influence access to care and opportunity to participate in research. With developments in universal health care and social policy, Canada has seen the health and well-being of its youngest citizens improve. For example, the decrease in infectious diseases that can be prevented with vaccines has been dramatic (PHAC, 2009). However, the benefits of this progress have not always applied equally, as some children are better able to enjoy a healthy life than others. Canadian children face differences in access to care based on language, culture, geography, income, and often a combination of these factors. Of particular importance given Canada's demography, research has documented social realities that expose children from indigenous communities to more risk factors for injury and some types of illness (Brownell *et al.*, 2008; Banerji *et al.*, 2009; Banerji, 2012; Irvine, 2012). Infants, children, and youth share a common vulnerability, but are not a homogenous group.

Children Need to be Protected

Children should be protected *through* research rather than *from* research. Children deserve to be protected from any harm that might occur during research and with use of new medications, but also from the risk associated with unauthorized use of medicines that are not known to be safe and effective for the population.

Children Need Research that Is Flexible and Adaptable

Pediatric research can be ethically and scientifically sound, and produce evidence-based options for medicines. Those who study and regulate medicines must be flexible in their approaches to science to meet the unique needs of children while still maintaining rigorous and robust scientific standards.

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Appendix: Additional Evidence Contributions

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To supplement its search of the literature, the Panel sought advice from leaders in pediatric medicines research. Specifically, the Panel reviewed published evidence from associations representing diseases and conditions that affect children and associations representing research and development of medicines for children. The objective of inviting these contributions was to ensure the Panel assessed recent and emerging standards, especially on topics that appear less frequently in published literature, such as patient and family engagement in research, and best practices in industry research. The response supplemented the literature search, validating the findings and pointing to additional high-quality published evidence.

The Panel contacted eight associations that represent children living with diseases. The following six organizations responded by providing evidence for the assessment:

- C¹⁷ Council
(Edmonton, AB) – www.c17.ca
- Canadian Child and Youth Health Coalition
(London, ON) – www.ccyhc.org
- Canadian Organization for Rare Disorders (CORD)
(Toronto, ON) – www.raredisorders.ca
- Institute of Families for Child and Youth Mental Health (IFCYMH)
(Vancouver, BC) – www.instituteoffamilies.ca
- JointHealth
(Vancouver, BC) – <http://jointhealth.org>
- Maternal Infant Child and Youth Research Network (MICYRN)
(Vancouver, BC) – www.micyrn.ca

The Panel contacted four associations that represent research and development of medicines for children. The following two organizations responded by providing evidence for the assessment:

- Canada's Research-Based Pharmaceutical Companies (Rx&D)
(Ottawa, ON) – www.canadapharma.org
- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
(Geneva, Switzerland) – www.ifpma.org

Assessments of the Council of Canadian Academies

The assessment reports listed below are accessible through the Council's website (www.scienceadvice.ca):

- Improving Medicines for Children in Canada (2014)
- Science Culture: Where Canada Stands (2014)
- Enabling Sustainability in an Interconnected World (2014)
- Environmental Impacts of Shale Gas Extraction in Canada (2014)
- Aboriginal Food Security in Northern Canada: An Assessment of the State of Knowledge (2014)
- Ocean Science in Canada: Meeting the Challenge, Seizing the Opportunity (2013)
- The Health Effects of Conducted Energy Weapons (2013)
- The State of Industrial R&D in Canada (2013)
- Innovation Impacts: Measurement and Assessment (2013)
- Water and Agriculture in Canada: Towards Sustainable Management of Water Resources (2013)
- Strengthening Canada's Research Capacity: The Gender Dimension (2012)
- The State of Science and Technology in Canada (2012)
- Informing Research Choices: Indicators and Judgment (2012)
- Integrating Emerging Technologies into Chemical Safety Assessment (2012)
- Healthy Animals, Healthy Canada (2011)
- Canadian Taxonomy: Exploring Biodiversity, Creating Opportunity (2010)
- Honesty, Accountability, and Trust: Fostering Research Integrity in Canada (2010)
- Better Research for Better Business (2009)
- The Sustainable Management of Groundwater in Canada (2009)
- Innovation and Business Strategy: Why Canada Falls Short (2009)
- Vision for the Canadian Arctic Research Initiative: Assessing the Opportunities (2008)
- Energy from Gas Hydrates: Assessing the Opportunities and Challenges for Canada (2008)
- Small Is Different: A Science Perspective on the Regulatory Challenges of the Nanoscale (2008)
- Influenza and the Role of Personal Protective Respiratory Equipment: An Assessment of the Evidence (2007)
- The State of Science and Technology in Canada (2006)

The assessments listed below are in the process of expert panel deliberation:

- The Future of Canadian Policing Models
- Canadian Industry's Competitiveness in Terms of Energy Use
- Memory Institutions and the Digital Revolution
- Wind Turbine Noise and Human Health
- STEM Skills for the Future
- The Potential for New and Emerging Technologies to Reduce the Environmental Impacts of Oil Sands Development
- RISK: Is the Message Getting Through?
- Timely Access to Health and Social Data for Health Research and Health System Innovation

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