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Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates

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The study of medications among pediatric patients has increased worldwide since 1997 in response to new legislation and regulations, but these studies have not yet adequately addressed the therapeutic needs of neonates. Additionally, extant guidance developed by regulatory agencies worldwide does not fully address the specificities of neonatal drug development, especially among extremely premature newborns who currently survive. Consequently, an international consortium from Canada, Europe, Japan, and the United States was organized by the Critical Path Institute to address the content of guidance. This group included neonatologists, neonatal nurses, parents, regulators, ethicists, clinical pharmacologists, specialists in pharmacometrics, specialists in clinical trials and pediatricians working in the pharmaceutical industry. This group has developed a comprehensive, referenced White Paper to guide neonatal clinical trials of medicines – particularly early phase studies. Key points include the need to base product development on neonatal physiology and pharmacology while making the most of knowledge acquired in other settings, the central role of families in research, and the value of the whole neonatal team in the design, implementation and interpretation of studies. This White Paper should facilitate successful clinical trials of medicines in neonates by informing regulators, sponsors, and the neonatal community of existing good practice.

PURPOSE

This document is intended to assist investigators and sponsors of studies that evaluate medicinal products in neonates. Since terminology for drugs, medicines, and medicinal products varies around the world, we have simplified these distinctions by using the term medicinal product throughout this document. While the focus of the document is on studies that will contribute to applications to regulatory authorities, the same principles apply to other studies involving neonates. In addition, this document may be useful for regulators who will be reviewing these studies. This document expands upon previous draft guidances entitled "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products: Guidelines for Industry" from the US Food and Drug Administration (FDA) (Dated December 2014) (1), the European Medicines Agency's (EMA) Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate (2), the International Conference on Harmonisation (ICH) E11 (3), and the Tri-Council Policy Statement (4) and other related documents by Health Canada. Studies of pharmacodynamics effect, clinical efficacy, safety and/or dose finding in neonates involve gathering clinical pharmacology information, such as information regarding a product's pharmacokinetics (PK) and pharmacodynamics (PD) that pertain to dose selection, optimization, and individualization. This document addresses general clinical pharmacology considerations for conducting studies in term and preterm neonates. That is, studies that generate information about dosing and preliminary safety for medicinal products evaluated in neonates. One goal of this document is to support the standardization and harmonization of approaches to studies in neonates worldwide in order to facilitate global development of new and existing medicinal products for this vulnerable population.

The scope of this document is clinical pharmacology information (e.g., PK, PD, and exposure response (E-R) relationships) that support findings of effect, efficacy, and safety and helps to identify appropriate dosages in term and preterm neonates. Since consideration of pharmaceutical quality and ethics influences many aspects of the design and implementation of clinical pharmacology studies, this document also discusses pharmaceutical quality, ethics, and participant welfare during studies. This document also describes the use of quantitative approaches (i.e., pharmacometrics) to employ knowledge about disease and E-R from relevant prior clinical