The development of therapeutics for neonates, both term and preterm, has lagged behind the development of safe and effective FDA regulated products for the treatment of older children and adolescents. Among the possible reasons for this therapeutic gap are: (1) the lack of cohesive pediatric networks and pediatric investigators experienced in pediatric trial requirements for studies (vaccines, nutrition, devices, drugs, etc.) being submitted to FDA; and (2) the need for scientific development in neonatology on, for example, the development of validated endpoints and alternate trial designs. Examples of these challenges are study design, appropriate endpoints, selection of short-term biomarkers, and other operational issues such as the prolonged duration of studies that would be able to assess outcomes. The 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) and the Institute of Medicine identified the continuing lack of prescribing information for neonates to be a problem, and charged the Office of Pediatric Therapeutics (OPT) with the responsibility for program development in this area. Specifically, FDASIA requires the staff of OPT to include at least one additional individual with expertise in neonatology through the year 2017.

Given the lack of funding for this position, OPT has proposed to meet this Congressional mandate through the combination of 2 important activities: (1) establish a neonatal subcommittee of the Pediatric Advisory Committee (PAC) to advise the Agency on general matters involving challenges to developing neonatal science and (2) when funds are available, hire a series of experienced neonatologists through available contracting mechanisms, each of whom during their tenure at FDA will address identified areas for development. To assist in developing the neonatal program, we have established a neonatal subcommittee of the PAC which is meeting for the first time on March 15, 2013.

OPT is asking the neonatal subcommittee to comment on how to approach the challenges that have been identified as impeding the advancement of neonatal science across all therapeutic areas (vaccines, nutrition, devices, drugs, etc.). These challenges broadly can be grouped into three categories – study design, study implementation and ethics. The discussion will focus on the first two topics, while recognizing that ethical issues will frame the discussion. Note that none of the topics will be subject to a vote, but rather are for general discussion. The discussion will be used to inform the development of a strategic plan for advancing neonatal science at FDA. In summary, the overall purpose of this initial neonatal subcommittee meeting is to discuss different programmatic strategies for advancing the scientific knowledge necessary for neonatal studies.

To stimulate the subcommittee’s thinking in preparation for the meeting, OPT provided some readings from the published literature. An annotated bibliography of those readings is found after the topics to be discussed.
Topics to be discussed:

Discuss the **challenges for the design of neonatal studies** to establish dosing, safety and efficacy across all developmental areas (drugs, biologics, devices, vaccines, nutrition, etc.). Among the issues to consider are: (1) defining the neonatal study population; (2) selecting and validating appropriate study endpoints and/or evaluation tools; (3) using short-term endpoints and/or biomarkers in lieu of long-term outcome studies; (4) impact of changes in drug absorption, distribution, metabolism, excretion; (5) impact of variability in drug response based on changes in transporters and/or receptors; (6) choosing an appropriate control group (including defining standard of care); (7) studying an off-label standard of care; (8) monitoring for safety; and (9) demonstrating long-term safety and/or efficacy through neurodevelopmental outcome studies.

Discuss the **challenges for the conduct of neonatal studies**, focusing on such issues as: (1) general study feasibility; (2) the existence of neonatal study networks; (3) the geographical distribution of term and preterm neonates; (4) the benefit-risk of multiple lab tests needing significant quantities of blood; (5) the role of imaging and how should it be obtained (transport, sedation, etc.); (6) the process and/or infrastructure for discussing and/or implementing clinical trial designs; (7) the reluctance of clinicians and parents to enroll neonates in studies; and (8) mechanisms for sharing data, including data from negative studies.

**Annotated Bibliography:**


In recent years, the use of adaptive design methods in pharmaceutical/clinical research and development has become popular due to its flexibility and efficiency for identifying potential signals of clinical benefit of the test treatment under investigation. The flexibility and efficiency, however, increase the risk of operational biases with resulting decrease in the accuracy and reliability for assessing the treatment effect of the test treatment under investigation. In its recent draft guidance, the United States Food and Drug Administration (FDA) expresses regulatory concern of controlling the overall type I error rate at a pre-specified level of significance for a clinical trial utilizing adaptive design. The FDA classifies adaptive designs into categories of well-understood and less well-understood designs. For those less well-understood adaptive designs such as adaptive dose finding designs and two-stage phase I/II (or phase II/III) seamless adaptive designs, statistical methods are not well established and hence should be used with caution. In practice, misuse of adaptive design methods in clinical trials is a concern to both clinical scientists and regulatory agencies. It is suggested that the escalating momentum for the use of adaptive design methods in clinical trials be slowed in order to allow time for development of appropriate statistical methodologies.

Despite many years of heavy use in premature and critically ill newborns, surprisingly few medications have been rigorously tested in neonatal multicenter randomized clinical trials. Little is known about the pharmacology of these drugs at various birth weights, gestational ages, and chronologic ages. This article describes a quality improvement approach to evaluating and improving neonatal intensive care unit (NICU) medication use, with an emphasis on adaptation of drug use to the specific clinical NICU context and use of system-based changes to minimize harm and maximize clinical benefit.


INTRODUCTION: The detection, assessment, understanding and prevention of adverse drug reactions (ADRs) are the primary aims of pharmacovigilance activities. Pediatric patients, especially all newborns and infants, are particularly at risk for experiencing drug-related adverse events. AREAS COVERED: This review briefly analyzes the physiological peculiarities of pharmacodynamic and pharmacokinetic aspects of drugs in newborns, infants and toddlers and children. It also deals with specific pediatric pharmacovigilance aspects, such as the frequent use of unlicensed and/or off-label drugs in neonatal intensive care units in European countries and in Australia. This review reports on European, American and Canadian data about the incidence and type of pediatric ADRs, particularly focusing on neonates, infants and toddlers. EXPERT OPINION: The awareness of pediatricians about the importance of reporting ADRs should be stimulated, new reporting systems should be encouraged and pediatric pharmacovigilance activities should be improved, first, by intensifying active post-marketing surveillance methods.


Although some drugs have been developed for the neonate, drug development for the least mature and most vulnerable pediatric patients is lacking. Most of the drugs are off-label or off-patent and are empirically administered to newborns once efficacy has been demonstrated in adults and usefulness is suspected or demonstrated in the older pediatric population. Few drugs are approved by the Food and Drug Administration for use in this population. The factors that prevent the demonstration of efficacy and safety in the newborn are discussed and a change in the current approach for neonatal drug studies is suggested.


Until approximately 15 years ago, sponsors rarely included children in the development of therapeutics. US and European legislation has resulted in an increase in the number of pediatric trials and specific label changes and dosing recommendations, although infants remain an understudied group. The lack of clinical trials in children is partly due to specific challenges in conducting trials in this patient population. Therapeutics in special populations, including premature infants, obese children and children receiving Neonatology extracorporeal life support, are even less studied. National research networks in Europe and the USA are beginning to address some of the gaps in pediatric therapeutics using novel clinical trial designs. Recent innovations in pediatric clinical trial design, including sparse and scavenged sampling, population pharmacokinetic analyses and 'opportunistic' studies, have addressed some of the historical challenges associated with clinical trials in children.


This article presents the executive summary of the presentations and discussions at the Workshop on Research in Neonatology sponsored by the National Institute of Child Health and Human Development and the American Academy of Pediatrics Section on Perinatal Pediatrics convened in January 2004. In this article, the scientific aspects are summarized, highlighting the current knowledge gaps and identifying research priorities with a focus on emerging technologies. In a separate article, issues concerning workforce needs and shortages and board-certification requirements are presented. Full-length articles on the presented topics will be published in the Journal of Perinatology.