

PhRMA Report for the Institute of Medicine

Challenges and Successes in Neonatal Drug Development

INTRODUCTION

At the Institute of Medicine's (IOM) April 28, 2011, meeting on *Pediatric Studies Conducted under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)*, the IOM requested that the Pharmaceutical Research and Manufacturers of America (PhRMA) outline the industry's experience with neonatal research, including challenges to successful completion of neonate studies. PhRMA is committed to the effective implementation of BPCA and PREA to advance the development of innovative pediatric treatments. The information contained in this report is a response to the IOM's request and represents the perspective of an expert working group involved in pediatric drug development from PhRMA's member companies.

Over the past many years, BPCA and PREA have successfully worked together to facilitate increased clinical research in children, including neonates (infants up to four weeks old) and young children. Prior to passage of these important provisions, approximately 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information. As of 2008, however, an estimated 50 to 60 percent of prescription drugs used to treat children had been studied for use in pediatric populations as a result of BPCA and PREA.¹ While clinical research has increased significantly with the enactment of these programs, challenges to engaging in pediatric research remain and, in particular, research in neonates and very young children.

Conducting medical research in neonates and young infants is highly complex and presents a host of scientific, physiological and medical, operational, and regulatory challenges. These challenges are especially magnified in the sick and/or premature neonates. The primary drivers of such challenges are often based on fundamental differences between growing and developing neonates and young infants (compared to adults), hence the need for specialized clinical trials to ascertain the safety and efficacy of medicines for these young children. Further, children, and in particular neonates, are a vulnerable population and study designs and procedures that may be appropriate for adults and older children may not be appropriate in neonates, causing significant constraints on the ability of sponsors to design and conduct clinical trials in this population.

¹ FDA Consumer and Health Information. Giving Medication to Children: Q&A with Dianne Murphy, MD, June 2009.

PHYSIOLOGICAL CHALLENGES AFFECTING DRUG DEVELOPMENT IN NEONATES

All major organs and systems, such as the skin, lungs, liver, kidney, muscle, circulatory, hematopoietic, and the central nervous system undergo significant and, often, rapid developmental changes in neonates, which may impact the way medicines are handled in the body and the way medicines affect the body. For example, total body water (TBW), extracellular water (ECW), total body fat, glomerular filtration rate (GFR), and blood volume are rapidly changing and affect drug distribution, metabolism, and pharmacokinetics (DMPK) in neonates. The human fetus develops in a highly controlled environment within the uterus and is totally dependent on the mother. Once the fetus is born, major organ systems undergo significant change and maturation in order to ensure independent existence and self-sufficiency. While birth triggers the most dramatic physiologic changes, many more subtle changes will continue to occur throughout the neonatal period and beyond, many of which could dramatically affect drug development.

The importance of these numerous organ system developmental changes is evident with the first breath. Respiratory changes at birth lead to decreased pulmonary resistance. This decreased resistance leads, not only to the expansion of lungs and their filling with air (which has a higher oxygen tension (pO_2) than the neonate was exposed to in the womb), but also to profound physiological shifts. Increased pO_2 that occur while breathing air causes pulmonary vasodilation and a drop in pulmonary arterial blood pressure. As a result, pulmonary blood flow increases from 35 mL/kg/min to 150–200 mL/kg/min.^{2,3} These and other types of physiological changes can have an impact on the pharmacokinetics (PK) and pharmacodynamics (PD) of administered drugs, which can present important challenges to the design and conduct of clinical studies in this population.

Blood Volume

In a neonate, blood volume is rapidly changing (total blood volume rises from approximately 100mL at 2.2 lbs to more than 7 times that amount [approximately 720 mL] at 19.8 lbs⁴) and affects drug DMPK. The range of neonate:adult half-life ratios exceeds the 3.16-fold factor

² Murphy JM. The Fetal Circulation. *Critical Care & Pain*. 5 (4). 2005.

³ Friedman AH, Fahey JT. The transition from fetal to neonatal circulation: normal responses and implications for infants with heart disease. *Semin Perinatol*. 17(2):106-21. 1993

⁴ Committee on Clinical Investigations, Children's Hospital in Los Angeles, CA; Baylor College of Medicine, Dallas, TX; and Cincinnati Children's Hospital Institutional Review Board, Cincinnati, OH. Adapted by: Jack R, Children's Hospital and Regional medical Center Laboratory, Seattle, WA, AUG 2001. Available at: http://docs.google.com/viewer?a=v&q=cache:E97n2EfSeXkJ:www.ucdmc.ucdavis.edu/clinicaltrials/documents/Blood_Draws_Maximum_Allowable.doc+www.ucdmc.ucdavis.edu/.../Blood_Draws_Maximum_Allowable.doc&hl=en&gl=us&pid=bl&srcid=ADGEESjfH5w5Pj9I3dMSulBgvcVYkrMt7FvPVMaa6ROwKJ5EPo6cKP7Hatfqp6A197gfThrfHCoDZ7MB61Q6F3RH1tAomzdZZMH5-QA7JMV2ASpB6TRfV7q6kv705xKEZoVu6LkoXae&sig=AHIEtbQKGESJhzinlrh6I3ZMfOqT6NY3zA&pli=1 Last accessed: 27SEP 2011.

commonly ascribed to interindividual PK variability and drugs administered to premature and full-term neonates tend to have a 3-9 times longer half-life than adults.⁵

Circulatory System

In the first 24–48 hours of life, a neonate shows a net loss of salt and water as it lowers its blood volume.⁶ In neonates, inadequate fluid intake can cause serious problems. Babies have a relatively higher body surface area: volume ratio compared with adults as well as a much more rapid respiratory rate and shallower breathing, which results in proportionately larger expiratory water loss. Further, rapid gastrointestinal (GI) transit times lower fluid re-absorption from the gut. Taken together, these coupled with low intracellular fluid volume, can precipitate rapid circulatory collapse. Therefore, drugs with the potential for further circulatory changes can have important consequences, some of which could be severely adverse to the wellbeing of the baby. Moreover, consideration of neonatal TBW composition and ECW compartments are informative in understanding how variables such as the Volume of Distribution (Vd) may determine whether or not loading doses should be instituted.

Body Composition

The body composition of an individual can play an important role in influencing the PK and PD of a drug. The distribution of body water in healthy neonates varies with the size of two main tissue components: the depot fat (which has low water content) and lean body mass, which holds most of the intracellular water. Muscle mass makes up the greatest part of the lean body mass. The changes in the ratio of intracellular water to the TBW in normal individuals follow the relationship between the muscle mass and the body weight.^{7,8} When compared to term infants, preterm infants whose postnatal age reach term have been found to have significantly lower lean body and fat mass, lower body weight and muscle and fat cross sectional area.⁹ Therefore, the total body composition of preterm and term infants may lead to differences in the PK/PD profile of drugs that redistribute into the fat and muscle, adding further complexity to the drug development process (design of clinical studies and interpretation of data) in neonates and infants. An important, but often overlooked confounder, is milk: a newborn's primary source of nutrition and hydration. It matters whether a young infant is wholly breastfed or is on commercial milk formula since the latter has a higher solute load. As noted below, the neonate has limited renal capacity to handle a high solute load and conserve fluid. Therefore, this may

⁵ Ginsberg G et al. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. *Toxicol Sci* 2002;66:185-200.

⁶ Behrman, RE and Kliegman, RM. Nelson Essentials of Pediatrics. W.B. Saunders Company. Philadelphia, USA: 2002.

⁷ Chumlea WC et al. Total body water data for white adults 18 to 64 years of age: The Fels Longitudinal Study. *Kidney International*. (56) 244–252, 1999

⁸ Deurenberg P et al. Multi-frequency impedance for prediction of extra cellular water and total body water. *British Journal of Nutrition*. 1995. 73,349-358.

⁹ Ahmad I et al. Body composition and its components in preterm and term newborns: A cross-sectional, multimodal investigation. *Am J Hum Biol*. 22(1):69-75; 2010.

need to be considered when planning a clinical trial involving the neonatal population, especially if the investigational product has the potential to alter fluid balance. We further highlight below select organ systems that undergo significant physiological changes during the neonate period and therefore require careful consideration for the conduct of clinical studies in neonates.

Renal Physiology

The newborn kidney does not perform as efficiently as an adult kidney, which can be particularly problematic, as immature renal function may delay excretion and affect PK for drugs primarily eliminated by the kidney. At birth, the renal cortex is relatively under-developed and does not fully mature until 12-18 months. Over the first 2-3 years of life, both GFR and tubular function increase (see Appendix A, Table 1). After birth, a marked increase in systemic blood pressure and decrease in renal vascular resistance results in elevated renal blood flow and consequent increases in GFR. Vasoactive factors, including glucocorticoids and prostaglandins play a role in the regulation of neonatal GFR and, therefore, in determining the kidney's ability to maintain homeostasis.^{10,11,12} Nephrogenesis may not be complete in infants born prematurely; hence, the maturity of a neonate can have a profound effect on glomerular filtration, renal tubular secretion and absorption, and the nephron's sensitivity to hormonal control. Therefore, the structural and functional differences of the neonatal kidney must be carefully considered when designing a study protocol.

Hepatic Physiology

Of particular importance in neonatal drug development is the role of hepatic maturation and its effect on drug metabolism and biotransformation. Complexity is increased with neonates in the drug development process because of a number of unique neonatal factors affecting the metabolism and biotransformation of drugs by a neonate: slower rate of biotransformation; marked interindividual variability in (with slower overall) elimination rate; variable maturational changes in metabolism and disposition at different gestational ages and with increasing postnatal age; presence of alternative biotransformation pathways compared with older children and adults; and increased vulnerability to pathophysiologic states.¹³ Enzymes involved in both Phase I (e.g., oxidation, reduction, and hydrolysis) and Phase II (e.g., conjugation) reactions are present at birth, but because the liver is immature, it cannot sufficiently metabolize or biotransform drugs until these liver enzymes approach adult levels. Premature neonates have an even greater impairment of enzymatic function, particularly with decreasing gestational age. Maturation of these liver enzymes occurs relatively quickly after birth

¹⁰ Musso CG et al. Renal physiology in newborns and old people: Similar characteristics but different mechanisms. *Internat Uro and Nephrol*. 2004. 36: 273-276.

¹¹ Jose PA. Neonatal Renal Function and Physiology. *Curr Opin Ped*. 1994. 6(2): 172-177

¹² EMA Discussion Paper On The Impact Of Renal Immaturity When Investigating Medicinal Products Intended For Paediatric Use (2004)

¹³ Nagourney BA, Aranda JV. Physiologic differences of clinical significance. In: Polin RA, Fox WN (Eds) *Fetal and Neonatal Physiology*, 2nd ed., Volume 1, Chapter 23, Philadelphia, WB Saunders Company, 1998; pp242.

regardless of the extent of prematurity; however, there is a wide range of variability in the rate of maturation.¹⁴

The cytochrome P450 (CYP450) monooxygenase system of hepatic microsomal oxidative enzymes is heavily involved in drug metabolism. Table 2 in Appendix A presents the key CYP450 enzymes as well as other enzymes affected by age-related immaturity. CYP450 is present in the midgestation fetal liver at 20 to 40% of adult levels. It is capable of mixed function oxidation of endogenous substances (eg., steroids).^{15,16} Low CYP450 enzyme activity in the fetus persists into the neonatal period with a direct correlation between activity and postconceptional age.^{15,17} The effect of this immaturity of CYP450 enzymes is prolonged serum half-life of drugs it metabolizes with wide interindividual variability for the first few days of life. Conversely, as CYP450 systems rapidly mature, the serum half-life of such drugs decreases as well as the interindividual variability. Within several weeks of birth, enzyme activity can surpass adult levels.¹⁵ an important complexity in developing novel drugs. Many neonates enrolled into clinical trials are ill and on multiple other drugs, which can lead to decreased rates of elimination by competition for enzymes that are only maturing to full capacity. A consequence for drug development in neonates is the need to closely monitor drug levels for several weeks after birth. Such close monitoring is often not necessary in older children or adults who, typically, have a more stable metabolic capacity.

Skin

With the advent of topical and transdermal formulations, another organ that provides a unique challenge in neonatal clinical drug development is the skin. The skin of a neonate is thinner than that of older infants and children. In preterm infants, there is almost no outer layer of the epidermis – the stratum corneum.¹⁸ However, the epidermis of the full-term neonate is relatively well developed. At birth, regardless of gestational age, the skin rapidly cornifies over a period of 2 to 3 weeks, which provides an effective epidermal barrier that protects the preterm neonate.^{19,20} However, the skin of a preterm neonate is fragile and susceptible to injury by topical agents.²¹ The thin epidermal layer allows absorption of drugs applied topically, which can readily lead to skin damage (e.g., burns) and increased exposure to the central compartment

¹⁴ Rane A. Basic principles of drug disposition and action in infants and children. In: Yaffe SJ (Ed) *Pediatric Pharmacology: Therapeutic Principles in Practice*. New York, Grune & Stratton, 1980;pp7-28.

¹⁵ Neims AH et al. Developmental aspects of the hepatic cytochrome P-450 monooxygenase system. *Ann Rev Pharmacol Toxicol* 1976;16:427.

¹⁶ Yaffe SJ et al. The presence of a monooxygenase system in human fetal liver microsomes. *Life Sci* 1970;9:1189.

¹⁷ Aranda JV et al. Hepatic microsomal drug oxidation and electron transport in newborn infants. *J Pediatr* 1974;85:534.

¹⁸ Rutter N. Percutaneous drug absorption in the newborn: hazards and issues. *Clin Perinatol* 1987;14:911.

¹⁹ Evans NJ, Rutter N. Development of the epidermis in the newborn. *Biol Neonate* 1986;49:74.

²⁰ Okah FA et al. Surface electrical capacitance as a noninvasive bedside measure of epidermal varrier maturation in the newborn infant. *Pediatr* 1995;96:688.

²¹ McCormack JJ et al. An in vitro comparison of the permeability of adult versus neonatal skin. In: Maibach HI, Boisits EK (Eds) *Neonatal Skin*. New York, Marcel Dekker, 1982.

(bioavailability). Although topical administration of drugs to neonates can eliminate some of the uncertainty around drug absorption that confounds oral administration in this age group,²² developing topical and transdermal formulations may not be technically feasible and adds complexity because of the developing portal of entry – the skin. Increasing drug absorption is seen in very premature neonates because of the high permeability and large surface area of their skin as well as the increased susceptibility of the immature skin to drug-induced trauma. Drug absorption through the skin decreases as the epidermis cornifies with increasing postnatal age. These changes and the need for more frequent drug monitoring in the premature infant add more complexity to the drug development process in neonates.

OPERATIONAL CHALLENGES AFFECTING DRUG DEVELOPMENT IN NEONATES

The following section outlines some of the many unique operational challenges that affect the design and conduct of clinical trials in neonates and very young infants:

Formulation Challenges

Developing appropriate drug formulations for neonates represents a significant operational hurdle. There is a need to carefully consider excipients (an inactive substance that serves as the vehicle or medium for a drug or other active substance), which may be toxic in neonates due to immature metabolism and elimination (for example benzyl alcohol, sodium benzoate, potassium sorbate, parabens, and propylene glycol) and require additional considerations when dosing neonates (see also *Hepatic Physiology* section above).^{23,24,25} A formulation must allow for accurate measurement and dosing and, in particular, provide for measurement of small incremental units and suitability of dosing for body weight / body surface area. Accuracy in dose volumes less than 1mL becomes critical as minute discrepancies may account for large changes in dose.²⁶ However, currently available types of dosing equipment do not permit the accurate measurement of volumes less than 0.1 mL.²⁷

Development of oral formulations for neonatal populations also needs to consider pharmaceutical properties such as viscosity and particle size (because of small sizes of feeding tube sizes (e.g., 5F, 8F)) as well as osmolarity, given the narrow range of acceptable osmolarity for oral formulations in neonates due to their developing GI tract as further highlighted above

²² Choonara I. Percutaneous drug absorption and administration. *Arch Dis Child* 1994;71:F73.

²³ Glasgow X, et al Hyperosmolarity in small infants due to propylene glycol. *Pediatrics* 1983;72:353-355

²⁴ Gershank J, et al. The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982;307:1384-1388

²⁵ Kumar P. Issues in the formulation of drugs for oral use in children: role of excipients. *Pediatric Drugs* 2002;4:371-379

²⁶ Mitchell AL. Challenges in pediatric pharmacotherapy: minimizing medication errors: dispensing errors www.medscape.com/viewarticle/421220_4.

²⁷ Parshuram C. Drug formulations that require less than 0.1 mL of stock solution to prepare doses for infants and children. *CMAJ* March 8, 2011 (183)4; March 8, 2011.

under section on **PHYSIOLOGICAL CHALLENGES AFFECTING DRUG DEVELOPMENT IN NEONATES.**

Dosing Challenges and Unmeasurable Loss of Drug

Frequent Dose Changes

Due to frequent changes in body weight and ongoing maturation of the renal, hepatic, and other organs and systems, neonates and very young infants typically require more frequent dose changes as compared to older children, which may complicate dosing regimens in clinical trials.

Third Party Dosing

An additional consideration that contributes to operational complexity in studies in this population pertains to third party administration of study drug. If a study drug is to be administered by a caregiver other than a health care provider, the formulations must be suitable for caregiver preparation and administration, with careful attention needed to create materials for informing and educating the caregiver.

Regurgitation and Suck/Swallow Coordination

Unmeasurable loss of drug further complicates oral medication administration due to regurgitation or need for gastric suctioning.²⁸ Medication that is administered via infant bottle also has some unmeasurable loss of drug as newborns can have uncoordinated suck and swallow.

Variable Drug Transit Time to Receptor

Drug delivery to the target receptor is a function of blood flow and plasma concentration, which, for intravenous (IV) medications, are dependent on a number of factors including administered dosage, volume, site of injection and IV flow rate. Administering medications via the IV route is a very important consideration and challenge in neonates. IV medication in neonates may be administered by IV push, antegrade injection, syringe infusion pump, and retrograde injection and can result in variable lag times to receptor site. IV medications with specific gravity less than that of IV fluid have the tendency to accumulate at high points of IV tubing and those with higher specific gravities tend to pool in loops of tubing both resulting in variable and inaccurate drug delivery. Doses that require small volumes are common in neonates and are difficult to administer. Injection site port distance to patient may take significant infusion time due to typically low infusion rates seen in infants and may lead to adsorption of medications in the administration sets (e.g., tubing). This may result in erratic dosing that may be clinically relevant. It is important to understand administration lag times in determining peak and trough levels of drugs in therapeutic monitoring and PK analyses that are essential in many clinical trials. Since

²⁸ Cotton CM, Turner BS, Miller-Bell M. Pharmacology in Neonatal Care in Merenstein GB, Gardner S. Handbook of Neonatal Care 6th Ed, 2006, Mosby St Louis, Missouri

the neonatal drug dose is typically administered in low volumes over a period (e.g., 30-60 minutes), the use of microbore tubing is often required to ensure successful drug delivery as such tubing allows for a more accurate administration under such circumstances.²⁸

Transit time to receptor also can be variable for orally administered drugs as GI motility and GI transit times in neonates can be impacted by feeding practices (continuous feeding vs. intermittent feedings) and feeding preference (breastmilk vs. formula).²⁹ Motility and GI transit time can be impaired during illness or as a result of adverse consequences of clinical care of the infant.

Additional Challenges Related to Route of Administration in Neonates

Intravenous Administration

Although IV fluids may be administered by umbilical vein or artery in neonates, medications via these routes are often restricted since these vessels are located centrally (unlike peripheral vessels) and complications such as thrombosis, air embolism, or omphalitis, while rare, can be immediately be life-threatening. Given these potential dangers, using the umbilical vessels may add to the challenge of IV medication administration in neonates. Besides the umbilical vessel, if IV access is available, IV push medications should be administered over a period of 1-2 minutes; post administration flush requires the same administration rate. IV pump administration has two approaches, one which includes priming the tubing with the medication to be delivered and therefore not requiring post administration flush and with the other approach, both drug and flush solutions are required to complete administration. The amount of study drug provided for preparation and administration would vary by method of IV pump administration and may complicate the estimation of exact amount of drug supply needed for the clinical trial and, thereby, hinder proper drug accountability at the site.²⁸

Intravenous access is frequently limited either due to loss of access (e.g., line occludes or goes interstitial) or competing priority for use of the line (e.g., multiple med administration) and thus can be unavailable for sampling at scheduled intervals in clinical trials. The limited IV access in the circumstance of multiple medications (as often occur when caring for sick neonates and very young infants) heightens the need for providing drug administration compatibility information, which is a significant need and challenge in the neonatal population. Having compatibility data on maintenance fluids more commonly used in neonates (usually higher dextrose solutions) for co-administration is also needed and has been an operational challenge in pediatric trials. In addition, limited IV access often results in extravasations of medications, which could lead to potentially serious adverse consequences, besides contributing to erratic dose administration.

²⁹ Fox E, Balis FM. Drug therapy in neonates and pediatric patients in Atkinson AJ, et al. Principles of Clinical Pharmacology, Second Ed. 2007, Elsevier Inc. London, UK

Topical Administration

Neonates, particularly premature infants, have immature skin (see section on **PHYSIOLOGICAL CHALLENGES AFFECTING DRUG DEVELOPMENT IN NEONATES**) and a larger skin surface area relative to body weight, which may result in increased absorption of topical medication with potential systemic effects. Plastic and other synthetic diapers can also increase absorption of topical drugs applied to the diaper area. A related but different challenge from other skin applications is the potential for toxicity either directly (e.g., skin erosion from tapes) or by absorption (e.g., the alcohol in skin wipes that could be neurotoxic). These challenges are potential confounders to data generated from neonatal clinical trials.

Increased Potential for Medication Error in Neonates

The neonatal patient is a vulnerable patient and has limited internal reserves to buffer errors. Medication errors are 3 fold higher in children than adults.³⁰ Neonates are particularly vulnerable to medication errors. For example, twenty percent of all pediatric medication errors occur in the first month of life.³¹ Medication errors are a significant problem in the NICU with reported incidence varying based upon definition. However, medication errors in the NICU are occurring at consistently higher rates than other areas of the hospital or other patient populations and are more likely to result in harm.³² It is important to note that this level of medication errors occurs during routine care of the sick neonate and likely relates to system design flaws and human fallibility coupled with the intensity of care and the fragility of the infants, among others. This level of medication errors could potentially confound the interpretability of data generated from clinical trials conducted in such settings.

Impact of Blood Sampling

The impact of blood sampling on hemoglobin (Hb) levels in neonates is an area of particular concern. On average, a sick neonate has approximately 39 ml of blood withdrawn for sampling in its first week of life.^{33,34} Blood sampling occurs for a host of reasons, including diagnosis and monitoring of therapy as well as meeting the ongoing clinical and diagnostic care needs, such as blood cultures, counts, chemistry, gases, among others. PK and PD blood sampling, added to the other sampling needs, can be a significant barrier and challenge to research given the blood volume requirements. For example, many IRBs and institutions have their own requirements for acceptable blood volumes for clinical trial sampling and these requirements vary between

³⁰ Kaushal et al. Medication errors and adverse drug events in pediatric inpatients *JAMA* 2001;285: 2114-2120

³¹ Ross LM, Wallace J, Paton JY. Medication errors in a paediatric teaching hospital in the UK: five years operational experience. *Arch Dis Child* 2000;83:492-497

³² Sharek PJ, et al., Adverse events in the neonatal intensive care unit: development, testing, and findings of an NICU-focused trigger tool to identify harm in North American NICUs. *Pediatrics* 2006;118:1332-1340

³³ Shannon, KM. Anemia of prematurity: progress and prospects. *Am J Pediatr Hematol Oncol* 12;14, 1990

³⁴ Howie SRC Blood sample volumes in child health research; review safe limits. *Bulletin of the World Health Organization* 2011;89;46-53. doi 10;2471/BIT.10.080010

institutions, which could add a layer of complexity to the design and conduct of clinical trials in neonates and very young infants.

For many of the reasons highlighted in this paper, blood sampling in neonates is technically challenging regardless of the method of sampling. For example, obtaining samples from indwelling lines requires discarding a small aliquot of blood to prevent dilution of sample with IV fluids. Besides blood loss as noted earlier, this amount of discarded blood may vary between institutions and between persons conducting the procedure. Therefore, results may be confounded by the degree of dilution in such samples. Long-term indwelling catheters to assist with sample collection put the neonate at an increased risk for infection and other catheter-related complications. Similarly, heel stick sampling is typically limited to small volume samples, which are prone to clotting and may be insufficient or inappropriate for some tests.

Even when sufficient and appropriate samples are obtained, results can vary by sampling site. For instance, hematocrit levels vary by collection site with values decreasing in order of capillary, arterial, and venous samples.³⁵ Therefore, lack of same source serial measurements can confound results, particularly in clinical trials. Further, iatrogenic blood losses may be treated with transfusions, which pose added risks and may also complicate the interpretation of study results.

In addition, some PK samples require sodium lithium, which may not be available as an anticoagulant in microtubes. Dry spot technology, which limits sample volumes, is not available for all needed assays.

Aside from these technical difficulties, most individuals consider blood sampling a painful or uncomfortable procedure. The need for repeated blood draws in PK/PD studies and the challenge of obtaining adequate blood samples (in both quantity and quality) for analyses are major deterrents to enrollment for both parents/guardians and investigators. Therefore, finding readily acceptable, easy, and adequate sampling methods remains a challenge in neonates and adds to the difficulty of conducting clinical trials in this population.

Missing Data

Missing data is common in neonatal clinical trials due to certain clinical care priorities, differing restrictions on permissible sample volumes between IRBs, and technical challenges in obtaining blood samples. Given these, it is especially crucial that protocols for neonatal clinical trials have a plan on handling missing data, which, if not adequately addressed, can result in uninterpretable data.

³⁵ Manco-Johnson M, Rodden DJ, Collins SM. Infection and hematologic diseases of the neonate in Merenstein GB, Gardner S. Handbook of Neonatal Care 6th Ed, 2006, Mosby St Louis, Missouri

Additional Operational Challenges

Standard of care in neonatal care settings have been reported to vary significantly even within small geographic regions, particularly in ventilation strategy, transfusion and discharge practices.^{36,37,38} The standard of care variations may lead to differences in clinical endpoints such as length on ventilation, length of hospitalization and intensive care unit stay that are not reflective of actual difference in physiology or treatment effect. If neonates are enrolled in clinical trials in an outpatient setting, care is needed to protect them from exposure to illness, as they remain immune incompetent. This is especially important when neonates are recovering from illness and during the fall and winter season when RSV outbreaks are common. Such outbreaks can significantly affect study enrollment and even the feasibility of an entire study.

The intensity of activities in the NICU coupled with frequent nursing, alarms and other sources of noise, traffic flow, and other factors can easily confound critical measurements when conducting clinical trials in neonates.

Moreover, many resource-limited settings have different standards and levels of sophistication in neonatal care (in both equipment and expertise). Yet, there may be a compelling need to enlist clinical study sites in such settings, which could require significant effort and resources to bring them to the acceptable level prior to the initiation of the clinical trial in order to minimize potential study confounders. Such site improvements have to be done in a manner that not only serves the purpose of the clinical trial but also is sustainable long after the clinical studies are finished. In other words, planning of the study in such settings must consider appropriate transfer of knowledge and technology, which for neonatal studies, could add significant cost.

Parental Consent

Unique developmental phenomena following the birth of an infant may create additional challenges to obtaining parental consent in neonatal studies as compared to consenting for studies conducted in older children. Pregnancy, childbirth, and care of the newborn are components of the complex process of attachment. The birth of a neonate can cause a period of psychological disorganization (or dysphoria) during which parent's normal coping mechanisms may be impaired. This dysphoric phenomenon may be worse should the neonate be born sick or develop an ailment shortly after birth. In the post-partum period, mothers may have transient deficits in cognitive function particularly in attention and memory function, which may not be conducive to the informed consent process. During this period of temporary dysphoria, there is a reciprocal heightened receptivity to support and assistance. Awareness of this vulnerability is

³⁶ Shoo KL, et al. Variations in Practice and Outcomes in the Canadian NICU Network 1996-1997. *Pediatrics* 2000;106:1070-1079

³⁷ Ringer SA, et al. Variations in transfusion practice in Neonatal Intensive Care. *Pediatrics* 1998;101:194-200.(doi:10.1542/peds.101.2.194

³⁸ Eichwald EC, et al. Inter-neonatal intensive care unit variation in discharge timing: influence of apnea and feeding management. *Pediatrics* 2001;108 (4):928-33

important to prevent an appearance of undue influence or even coercion to participate in a clinical trial.³⁹

REGULATORY CONSIDERATIONS FOR PEDIATRIC RESEARCH IN THE UNITED STATES

As highlighted throughout this paper, pediatric drug development, particularly as it applies to the neonatal age group, poses unique challenges due to the fundamental physiological differences between growing and developing children and adults as outlined above and therefore requires specialized clinical trials to ascertain the safety and efficacy of drugs for children. Children, and neonates in particular, are a vulnerable population and study designs and procedures that are appropriate in adults and older children may not be appropriate in neonates therefore causing significant constraints on the study design and conduct.

Children, in general, represent a small target population for the proposed drug use, and are a challenge to recruit and retain in clinical trials. On balance, the combination of the significantly greater difficulty in conducting the necessary research and the small population size historically reduced the overall market incentive to conduct trials that would have provided the information necessary for pediatric labeling. Hence, incentives were created under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) to encourage pediatric development and the inclusion of pediatric information in drug product labeling.

The increase in pediatric studies is fully consistent with the intent of the US Congress in enacting BPCA and PREA. Such increase also is a testimony to the FDA's willingness to work with sponsors to design, amend, and review pediatric studies that result in meaningful information to be added to product labeling. Given this remarkable outcome, BPCA and PREA must be reauthorized permanently in the interest of this young and vulnerable population.^{30,40,41,42,43,44}

Timely and iterative communications between sponsors of pediatric studies and the FDA are critical to the success of pediatric drug development programs.

³⁹ Siegel R, Gardner SL, Merenstein GB Families in Crisis: Theoretical and practical considerations in Merenstein GB, Gardner S. Handbook of Neonatal Care 6th Ed, 2006, Mosby St Louis, Missouri

⁴⁰ FDA Website: Pediatric Drug Development

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>).

⁴¹ Kaushal, R. *et al.* Medication errors and adverse drug events in pediatric inpatients. *JAMA* 285, 2114–2120 (2001).

⁴² Turner, S., Nunn, A. J., Fielding, K. & Choonara, I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr.* 88, 965–968 (1999).

⁴³ Neubert, A. *et al.* The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf.* 27, 1059–1067 (2004).

⁴⁴ Horen, B., Montastruc, J. L. & Lapeyre-Mestre, M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br. J. Clin. Pharmacol.* 54, 665–670 (2002).

From our perspective, FDA's experience with the conduct of pediatric programs can vary by review division and therapeutic area. The Pediatric and Maternal Health Staff is the only group within the Center for Drug Evaluation and Research (CDER) dedicated to pediatric issues and review divisions often have to balance competing priorities that may prevent them from being able to focus on the review of pediatric programs.

The ability to conduct neonatal or other pediatric studies depends largely on the epidemiology of the disease. Diseases and conditions that are common in adults are often important, but much less common and more heterogeneous, in childhood. The relative rarity of some childhood conditions as they exist in neonates lessens the likelihood that sufficient patient numbers will be available to conduct adequate and well controlled studies, which may qualify for labeling. Although PREA grants FDA the authority to waive, partially waive, or defer required studies for certain conditions and age groups, increased transparency and consistency in how such decisions are made would facilitate the planning and conduct of pediatric studies.

Furthermore, when studies are deemed feasible, detailed elements of the study design need to be based on acceptable practices and consensus within the scientific and clinical research community. Elements such as "pediatric appropriate" formulation, sampling frequency, endpoints (see section on **OPERATIONAL CHALLENGES AFFECTING DRUG DEVELOPMENT IN NEONATES**) must be evidence-based to facilitate the successful conduct of a pediatric program.

CONCLUSION

Neonates and young infants are a particularly vulnerable population. Conducting research in this population has many regulatory, operational, and clinical challenges, and significantly more so when they are sick or premature. Every effort should be made to encourage and incentivize appropriate research in this patient population.

BPCA and PREA have been tremendously successful in spurring clinical research in pediatric patients, including neonates and young children. As of late August 2011, a search of ClinicalTrials.gov website using the keyword "neonate" or "newborn" showed that 1416 trials were completed or ongoing. Prior to BPCA and PREA, clinical trials in neonates were sparse, which led to clinical practice in newborns largely based on trial and error or using a variety of estimations when dosing children with medicines developed for the adult population.

Drug development in neonates has led to a generation of new/enhanced safety information, new understanding of PK differences, expansion of appropriate age ranged for a host of medicines, establishment of efficacy based on empirical data, restriction of age range based on PK and/or efficacy data, and data on long-term effects of a drug on growth and development. Generating appropriate clinical trial data that informs labeling for neonates provides physicians the confidence to prescribe the appropriate medication, provides parent with the assurance that the right medicine is being used for their child and ultimately helps to enhance public trust

in the health care system. Appendix B shows a list of medicines labeled for neonates and young infants based on data generated from clinical development stimulated by BPCA and PREA.

The current interplay between BPCA and PREA has encouraged and increased important drug development efforts in neonates as a component of an overall drug development program. These programs have provided an impetus for promoting drug development in neonates and must be reauthorized permanently in the interest of patients. PhRMA companies are proud of the work that has been done thus far in advancing neonatal clinical research and are committed to further advancement of pediatric research in the years to come.

APPENDIX A

Table 1: Age-specific Parameters of Renal Function

Normal values	Neonate	Adult
GFR	10-20 mL/min/m ²	60-80 mL/min/m ²
- premature	0.7-0.8 mL/min/m ²	
- at birth	1-2 mL/min/m ²	
- at 1 month	50 mL/min/m ²	
Maximum urine concentration	450-600 mosmol/L	1400 mosmol/L
Plasma creatinine	neonate ~18-35 µmol/L	- male ~55-120 µmol/L
		- female ~45-95 µmol/L
		- pregnant female ~30-80 µmol/L
pH	7.35	7.4
HCO ₃	20 mmol/L	25 mmol/L

Table 2: Developmental Changes in CYP450 Enzymes⁴⁵

Enzyme	Substrate	Developmental Changes
CYP 1A2	APAP	Not present in fetal liver Adult level by 4m
CYP 2C9 CYP 2C19	Diclofenac Phenytoin Diazepam	Not present in fetal liver Adult level by 12m
CYP 2D6	Codeine Ondansetron Amitriptyline	Low levels in fetal liver 20% of adult level by 1m Adult levels by 3m
CYP 3A4	APAP Diazepam Midazolam	Low levels in first month Adult levels by 12m
CYP 3A7	Dihydropyrimidines	70% of adult levels at birth
UDP-GT	APAP Morphine Lorazepam	Adult level by 6-18m
Sulfotransferase	APAP	Activity for some isoforms may exceed adult values in infancy
N-acetyltransferase	Clonazepam	Adult activity by 1-3yrs

⁴⁵ Yaster, M Comprehensive Course in Pediatric Drug Development. PERI, Arlington, VA, 2010.

APPENDIX B

Results of Clinical Drug Development in Neonates and Infants

Drug	Outcome
Gabapentin*	Higher oral clearance in infants >1mon
Clopidogrel*	No reduction in all-cause mortality or shunt-related morbidity in infants <3 months
Drotrecogin alfa (activated)*	Safety and efficacy not established in children, including 30 neonates <1 month
Lamivudine*	Substantially reduced oral clearance in infants <3mon olds and particularly in 1-wk old neonates
Esomeprazole Na	Extended indication from adults to pediatric patients ≥1mon; effectiveness not established in patients <1mon
Nitric oxide	Not indicated for prevention of bronchopulmonary dysplasia in preterm neonates ≤34 weeks gestation
Ioteprednol etabonate & tobramycin	Efficacy not established in neonates and infants (0-≥3mon)
Famciclovir	PK studied in infants ≥1mon; data insufficient to support use in the treatment of chicken pox or infections due to HSV
Topiramate	Effectiveness not established in infants ≥1mon; trials suggest some adverse reactions/toxicities not observed in older children/adults eg., growth/length retardation, lab abnormalities
Zidovudine	Dosing provided for neonates/infants 4wks to <6wks weighing 4 to <9kg
Zidovudine	Dosing provided for infants ≥6wks
Rocuronium	Expanded indication from ≥3mons down to ≥0
Caspofungin	Extended indication from adults down to ≥3mon
Nevirapine	Dosing provided for neonates/infants from >15d; safety was evaluated in neonates ≥2wks; safety, PK, virologic and immunologic responses evaluated in HIV-infected infants ≥3mon; safety and PK evaluated in neonates/infants 15d to <3mon; efficacy evaluated in infants ≥3mon
Fluocinolone	Extended age range down to 3mon
Hydrocortisone butyrate	Effectiveness established in infants ≥3mon; information provided on HPA axis suppression in infants ≥3mon with moderate-to-severe atopic dermatitis affecting ≥25% BSA; studies waived in neonates/infants 0-<3mon
Emtricitabine	Efficacy preventing/treating HIV in neonates/infants to 3mon could not be determined after a PK study in 20 neonates born to HIV positive mothers; dosing information in 0-3mon and additional safety and PK parameters provided
Desonide	Effectiveness established in infants ≥3mon; not recommended in patients <3mon
Desonide	Effectiveness established in infants ≥3mon; not recommended in patients <3mon
Brinzolamide	IOP-lowering efficacy not demonstrated in neonates/infants ≥4wks with bid dosing
Ritonavir	Extended age from 2yrs down to 1mon
Emtricitabine	Safety and effectiveness shown in infants ≥3mon
Ertapenem	Approved use down to 3mon; not recommended <3mon – no data available
Ondansetron	Established dosing in surgical patients down to 1mon from 2yrs; CI in patients

Drug	Outcome
	1-4mon is slower and the half-life is ~2.5-fold longer than patients >4mon; patients <4mon on drug need close monitoring
lansoprazole	Effectiveness not established in neonate/infants ≥1mon; information obtained on PK parameters in neonates to <1yr
Fenoldopam	Indicated for in-hospital, short-term (up to 4h) reduction in BP in neonates/infants <mon (at least 2kg) onward; information provided on PK, dose, and AE profile
Remifentanyl	Safety and efficacy for maintenance of anesthesia from birth to 1yr; recommended dosing guidelines for maintenance of anesthesia for patients from birth to 2mon; CI observed in neonates was highly variable - ~2x higher than young, healthy adults
Famotidine	Infants up to 3m require lower dose due to inability to metabolize the drug; patients 0-3mon had CI values 2-4-fold less than those in older patients and adults
Didanosine	Safety and effectiveness established down to 2wks
Stavudine	Safety and effectiveness established down to birth; established dose for newborns from birth to 13d
Betamethasone	HPA axis suppression shown in ≥3mon infants being treated for atopic dermatitis
Sotalol	Information provided on PK and PD in neonates/infants ≥3d
Propofol	Maintenance of anesthesia down to 2mon from 3yrs
Multivitamin infusion	Approved for infants/neonates down to newborn
Mycophenylate	Approved use down to 3mon as combination regimen with cyclosporine and corticosteroids
Levothyroxine	Approved down to newborn
Chlorhexidine/isopropyl alcohol	Indication (skin prep prior to surgery) approved down to 2mon; do not use in patients <2mon
Ranitidine	Small studies in newborns 0-1mon receiving ECMO did not demonstrate efficacy, but provided information on dose and PK
Fluticasone propionate	Extended age from 5yrs to 3mon
Abacavir	Labeling for ≥3mon; information provided on dose, efficacy, PK parameters, and AE profile

*Not in FDA Pediatric Labeling Changes through July 18, 2011 table. | FDA. Pediatric Labeling Changes through July 18, 2011. Available at:

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf>. Last accessed: 1 SEP 2011.