
General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**July 2022
Clinical Pharmacology**

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Guidance for Industry

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Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors of investigational new drug applications (INDs) and applicants of new drug applications (NDAs), biologics license applications (BLAs),² and supplements to such applications who are planning to conduct clinical studies in neonatal populations.^{3,4,5}

This guidance provides recommendations for neonatal clinical pharmacology studies, whether the studies are conducted pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act

¹ This guidance has been prepared by the Neonatal Clinical Pharmacology Working Group in the Office of Clinical Pharmacology, Office of Translational Sciences, in the Center for Drug Evaluation and Research (CDER) in collaboration with the Division of Pediatric and Maternal Health in the Office of New Drugs, CDER, the Office of Pediatric Therapeutics in the Office of the Commissioner, and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² This guidance is applicable to BLAs submitted under section 351(a) of the Public Health Service Act (PHS Act). For the Agency's thinking regarding considerations for BLAs submitted under section 351(k) of the PHS Act, see the FDA guidance entitled *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. For additional information on biosimilar applications, see the FDA guidance entitled *Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)* (September 2021).

³ Hereafter in this guidance, the term *sponsor* refers to *sponsors and applicants*.

⁴ For purposes of this guidance, references to *drugs* includes drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) (21 U.S.C. 355) and biological products licensed under 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)) that are regulated as drugs. Hereafter, the term *drug* will be used to refer to all such products.

⁵ For more information, see the FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014), which addresses general clinical pharmacology considerations in all pediatric subpopulations, including neonates. When final, this guidance will represent the FDA's current thinking on this topic.

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(FD&C Act),⁶ section 505B of the FD&C Act,⁷ or neither. Effectiveness, safety, or dose-finding studies in neonates involve assessing clinical pharmacology information, such as information regarding a product's pharmacokinetics (PK) and pharmacodynamics (PD) to inform dose selection and individualization. As such, the general considerations described in this guidance apply to any neonatal studies which incorporate clinical pharmacology assessments. This guidance does not discuss the timing to initiate neonatal studies. Questions regarding the appropriate timing for the initiation of neonatal studies should be discussed with the relevant FDA review division.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

In 2012, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) were made permanent under Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA).⁸ FDASIA requires that if a written request issued under BPCA for pediatric studies does not request studies in neonates, the written request must include the rationale for not requesting such studies.⁹

Given that most drugs used in neonatal intensive care units (NICUs) are used off-label, it is important that drug information be obtained in neonates to address gaps in neonatal labeling. In addition, therapies should be developed for conditions unique to neonates. New approaches to the study of drugs in neonates should consider the diversity of the patient population and underlying conditions that are cared for in NICUs.

During in utero development, there are significant physiological changes in the fetus involving the maturation of organs and tissues, including enzyme systems, receptors, transporters, and neurotransmitters. The normal developmental trajectory of these systems is altered by preterm delivery. Postnatal development can also be adversely affected by concurrent illnesses, resulting in altered maturation of organs and tissues and affecting the systems responsible for product

⁶ Section 505A of the FD&C Act is often referred to by the acronym of the Act that created it, the Best Pharmaceuticals for Children Act (BPCA).

⁷ Section 505B of the FD&C Act is often referred to by the acronym of the Act that created it, the Pediatric Research Equity Act (PREA).

⁸ Title V Sec 501(a) of FDASIA can be found at <https://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf>.

⁹ See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

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absorption (A), distribution (D), metabolism (M), and excretion (E), known collectively as ADME.

Gestational age (GA) at birth, postnatal age (PNA), and other factors (e.g., concurrent illness, underlying disease) can independently alter the pharmacokinetic (exposure) and pharmacodynamic (response) characteristics of a drug, which are essential components of the clinical pharmacology assessment. For example, a neonate born at 24 weeks gestation who is 4 weeks PNA is physiologically different compared to a 28-week gestation neonate who has just been born. Therefore, the clinical pharmacology assessment should include a range of gestational ages, postnatal ages, and body weights, if feasible, unless the drug is intended to treat only a specific neonatal subpopulation.

Leveraging prior knowledge and data obtained from adult, preclinical,¹⁰ and other pediatric studies coupled with innovative quantitative approaches can help predict neonatal doses and optimize clinical trial design. Using quantitative approaches such as population pharmacokinetics (population PK) and physiologically based pharmacokinetic (PBPK) modeling is critical to inform neonatal drug development.

Detailed planning of neonatal studies should include input from a multidisciplinary team involved in neonatal care, including parents and NICU nurses, in the early stages of study design to provide their perspectives of study feasibility and the potential impact of study participation on neonates and their families.

For studies conducted to fulfill PREA requirements, the submission of the initial pediatric study plan (iPSP)¹¹ is intended to encourage sponsors to consider pediatric studies early in product development, and when appropriate, begin planning for these studies. The iPSP should include plans for neonatal studies unless a waiver of the PREA requirements for the neonatal population is sought. If the iPSP contains neonatal studies, the plan should include: (1) an outline of the neonatal study or studies that the sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups (including neonatal subpopulations if relevant), relevant endpoints, and the statistical approach); (2) any request for a deferral or partial waiver if applicable, along with any supporting information; and (3) other information recommended in relevant FDA guidance.

III. DEFINITIONS AND SUBGROUP CLASSIFICATIONS

Historically, the neonatal period was defined as 28 days from delivery. However, the survival of preterm infants as premature as 22 to 23 weeks gestation at birth has necessitated a re-evaluation

¹⁰ We support the principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

¹¹ See the FDA guidance entitled *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

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of this historical definition, due to the weeks or months of NICU care required for maturation and growth to term equivalency.

In this guidance, as in the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018), the *neonatal period* is defined for the term and post-term newborn as the day of birth plus 27 days, and for the preterm newborn, as the day of birth and ending at the expected date of delivery plus 27 days. This definition is consistent with consideration of the neonatal age group to include individuals up to 44 completed weeks post-menstrual age (PMA). PMA has been used to date a gestation from the first day of the mother's known or reported last menstrual period and can be used either to define the GA at birth or the GA at birth plus the PNA. On the day of birth, PMA is equal to the GA.

Furthermore, the neonatal population can be categorized into subgroups based on a variety of factors. The following are examples of classifications:

Classification based on GA at birth:

- Preterm neonates at the border of viability: 22 to <24 weeks GA¹²
- Extremely preterm neonate: 24 to <28 weeks GA¹³
- Very preterm neonate: 28 to <32 weeks GA¹⁴
- Moderate-to-late preterm neonate: 32 to <37 weeks GA¹⁵
- Term neonate: 37 to <42 weeks GA¹⁶
- Post-term neonate: ≥42 weeks GA at birth¹⁷

Classification based on weight at birth:

- Preterm neonates at the border of viability: <600 grams
- Extremely low birth weight neonates (ELBW): <1000 grams
- Very low birth weight neonates (VLBW): <1500 grams
- Low birth weight neonates (LBW): <2500 grams

¹² Cummings, J and Committee on Fetus and Newborn, 2015, Antenatal Counseling Regarding Resuscitation and Intensive Care Before 25 Weeks of Gestation, *Pediatrics*, 136(3):588-595.

¹³ Howson CP, M Kinney, and JE Lawn, editors, March of Dimes, The Partnership for Maternal, Newborn and Child Health, Save the Children, World Health Organization. *Born Too Soon: The Global Action Report on Preterm Birth*. Geneva: World Health Organization, 2012, https://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf, accessed June 14, 2021.

¹⁴ Ibid.

¹⁵ Ibid.

¹⁶ The American College of Obstetricians and Gynecologists, 2013, ACOG Committee Opinion No 579: Definition of Term Pregnancy, *Obstet Gynecol*, 122(5):1139-1140.

¹⁷ Ibid.

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Other classifications:

- Small for gestational age (SGA) neonates: Birth weight less than the 10th percentile
- Large for gestational age (LGA) neonates: Birth weight greater than the 90th percentile
- Intrauterine growth restriction (IUGR): Fetal weight (by ultrasound) less than the 10th percentile

Depending on the needs of an individual drug development program, the classifications described above could be used to define more homogeneous groups of neonates for inclusion in a trial or for stratifying neonatal subgroups enrolled in a trial. Other classifications may be appropriate if supported by rationale and references. It should be noted that growth charts can vary depending upon the geographical region and should be accounted for in classification.

When designing studies, it is important to consider stratifying the neonatal population to address heterogeneity. While neonates can be grouped by GA and/or weight at birth, PNA is another important variable to consider for stratification, as there are significant ADME changes related to PNA. For example, ADME characteristics can be very different for an extremely preterm infant in the first few hours of life compared to the first few days after birth and compared to more than a week after birth. These characteristics also are different for an extremely preterm infant compared to a moderate-to-late preterm infant. All of these factors are important in the context of the specific drug being studied, as they could directly affect organ and tissue responsiveness and drug disposition. In addition, disparities at both ends of the growth spectrum (e.g., SGA, LGA) can impact developmental physiology and pharmacology. If stratification is based on birth weight, LGA infants might be assumed to be more mature than they actually are based solely on weight criteria.

IV. GENERAL CONSIDERATIONS

Before initiating neonatal clinical pharmacology studies, the sponsor should assess the available scientific information regarding the mechanism of action of the drug, the PK of the drug, and the ontogeny of any organs and tissues that are involved in the predicted response to the drug or its metabolites. This scientific information can be derived from several sources, including applicable animal models, in vitro studies, and other potentially relevant clinical studies. This information can be used to develop models and perform simulations to inform neonatal clinical pharmacology studies.

Model development requires an in-depth knowledge of the ontogeny of the target organs and tissues as well as the ontogeny of the organs and tissues involved in the ADME of the drug and its metabolites. The current gaps in this scientific information in neonates can limit the full potential of the application of modeling and simulation in this context. However, as this scientific information becomes available, these data can be incorporated into models to inform and update the design of neonatal clinical pharmacology studies.

Neonates can be uniquely susceptible to drugs that cross the blood-brain barrier and drugs that alter general physiologic parameters. Because of developmental and growth considerations, for a

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specific drug it could be recommended to follow neonates for potential safety issues longer than for older children and adults. While long-term endpoints could be recommended to assess the safety and efficacy of drugs administered in the neonatal period, it is also important to develop short-term endpoints where feasible. Sponsors are encouraged to consult with FDA on this issue early in the development process.

A. PK

Adequate characterization of the PK of a drug can help to optimize dose selection for neonatal studies. In the neonatal population, inter- and intra-individual variability in measures are affected by multiple factors, for example, body size, abnormalities in fetal growth, maturation (PMA and PNA), underlying illnesses, and concomitant medications. Factors that can contribute to variability should be documented as part of the trial for later analysis. To account for this variability, it could be important to evaluate the product across a wide spectrum of PMA and PNA of neonates if the indication to be studied is relevant in those populations. Sponsors are encouraged to consult with FDA on this issue early in the development process.

1. Absorption

There are multiple developmental changes in neonates that can affect absorption. Many of these factors have unique ontogenic differences in the neonatal population which should be taken into consideration in any neonatal trial (e.g., gastric acidity, rates of gastric emptying and gastrointestinal motility, surface area of the absorption site, gastrointestinal metabolizing enzyme systems, gastrointestinal permeability, biliary function, transporter expression, mode of administration, type of enteral feeding, and cutaneous maturation).

Developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, can affect absorption patterns of medicinal products delivered by intramuscular, subcutaneous, or percutaneous routes.

In general, when designing pharmacokinetic studies in neonates, sponsors should consider that the absorption for products administered non-intravenously could be different in the neonatal population compared to older children.

2. Distribution

Distribution of a drug can be affected by changes in body composition, such as changes in total body water and adipose tissue, which are not necessarily proportional to changes in total body weight. At birth, neonates have a higher total body water content, which is primarily extracellular. The proportion of total body water, as a percentage of body weight, increases with decreasing PMA. After birth, term neonates generally lose up to 10 to 15 percent of their total body water in the first postnatal week followed by a return to birth weight by 10 to 14 days PNA. For preterm neonates, the total body water loss could be greater than in term neonates, and the recovery of birth weight usually takes longer. Blood flow to an organ or tissue (e.g., brain, liver) can differ between term and preterm infants. Blood flow in neonates can also differ from blood

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flow in older pediatric and adult populations. These differences could result in altered tissue distribution of the drug.

Plasma protein-binding and tissue-binding changes arising from changes in body composition with postnatal growth and development can also influence drug distribution. The concentrations of circulating proteins and the degree of protein binding of a drug can be lower in preterm and term infants compared to older children and adults. In addition, serum protein concentrations can remain low for weeks in the critically ill preterm infant. For drugs that are protein bound, preterm infants can have an increased exposure to free, unbound concentrations of the drug which can impact its efficacy and safety.

When designing pharmacokinetic studies in neonates, sponsors should consider the following when feasible:

- Characterize protein binding, particularly for drugs with high protein binding. For drugs that are highly protein bound, collect serum protein levels in neonates to evaluate the potential impact on PK (see section G.1. Application of Quantitative Approaches).
- Given the risk of hyperbilirubinemia in neonates, it is important to assess the displacement of bilirubin from the albumin binding site if the drug is likely to bind to albumin.

3. Metabolism

Drug metabolism commonly occurs in the liver, but can also occur in the blood, gastrointestinal tract, kidney, lung, and skin. Information on the metabolism of specific drugs in neonates is generally limited. Each metabolic pathway has unique ontogenic characteristics that should be considered when designing clinical pharmacology studies in neonates. In addition, some metabolizing enzymes can have different expression and activity in neonates compared to older populations (e.g., CYP3A7 is higher and CYP3A4 is lower in neonates compared to adults).^{18,19}

Before conducting a clinical pharmacology study in neonates, sponsors should consider the following:

- To plan neonatal studies, a thorough review of scientific literature and the available data from adults or older pediatric subjects should be conducted to obtain information about the metabolic pathways relevant to the specific drug.

¹⁸ Lacroix D, M Sonnier, A Moncion, G Cheron, and T Cresteil, 1997, Expression of CYP3A in the Human Liver - Evidence that the Shift Between CYP3A7 and CYP3A4 Occurs Immediately After Birth, *Eur J Biochem*, 247(2):625-34.

¹⁹ Fanni D, R Ambu, C Gerosa, S Nemolato, M Castagnola, P Van Eyken, G Faa, and V Fanos, 2014, Cytochrome P450 Genetic Polymorphism in Neonatal Drug Metabolism: Role and Practical Consequences Towards a New Culture in Neonatology, *Int J Immunopathol Pharmacol*, 27(1):5-13.

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- As the postnatal ontogeny of many of these metabolic pathways has not been fully elucidated, it could be recommended to perform additional in vitro or preclinical studies.
- When appropriate, microdosing studies in neonates can be considered to provide preliminary pharmacokinetic information and assess for potential ontogenic differences in the metabolic pathway compared to older populations.^{20,21,22}
- Modeling and simulation approaches should be considered early to inform dosing and account for available information (e.g., ontogeny, PK in older pediatric age groups).

4. Excretion

Drug excretion by the kidneys is the net result of glomerular filtration, tubular secretion, and tubular reabsorption. The glomerular filtration rate (GFR) is low in neonates, particularly in those born before 32 weeks PMA and increases rapidly after birth.^{23,24,25} For drugs that are primarily renally excreted, systemic exposure of a drug is related to both PMA and PNA.²⁶ Pulmonary and gastrointestinal/biliary routes of excretion can also be important for certain drugs and could be affected by the ontogeny of those organ systems.

Before conducting a clinical pharmacology study in neonates, sponsors should consider the following:

²⁰ Roth-Cline M and RM Nelson, 2015, Microdosing Studies in Children: A US Regulatory Perspective, *Clin Pharmacol Ther*, 98(3):232-3.

²¹ Mooij MG, E van Duijn, CAJ Knibbe, K Allegaert, AD Windhorst, J van Rosmalen, NH Hendrikse, D Tibboel, WHJ Vaes, and SN de Wildt, 2017, Successful Use of [¹⁴C]Paracetamol Microdosing to Elucidate Developmental Changes in Drug Metabolism, *Clin Pharmacokinet*, 56(10):1185-1195.

²² Ethical considerations for conducting a microdosing study are similar to those for a single-dose pharmacokinetic study. See the FDA draft guidance *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014) for more information. When final, this guidance will represent the Agency's current thinking on this topic.

²³ Anderson BJ and NHG Holford, 2008, Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics, *Annu Rev Pharmacol Toxicol*, 48:303-32.

²⁴ Rhodin, MM, BJ Anderson, AM Peters, MG Coulthard, B Wilkins, M Cole, E Chatelut, A Grubb, GJ Veal, MJ Keir, and NHG Holford, 2009, Human Renal Function Maturation: A Quantitative Description Using Weight and Postmenstrual Age, *Pediatr Nephrol*, 24:67-76.

²⁵ Mahmood I and MA Tegenge, 2019, A Comparative Study Between Allometric Scaling and Physiologically Based Pharmacokinetic Modeling for the Prediction of Drug Clearance From Neonates to Adolescents, *Pediatr Pharmacol*, 59(2):189-197.

²⁶ Wang J, SS Kumar, CM Sherwin, R Ward, G Baer, GJ Burckart, Y Wang, and LP Yao, 2019, Renal Clearance in Newborns and Infants: Predictive Performance of Population-Based Modeling for Drug Development, *Clin Pharmacol Ther*, 105(6):1462-1470.

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- The ontogeny of transport systems, particularly those involved in active transport, have not been well elucidated in neonates. When relevant to the specific drug, ontogenic differences in a transport system could have an impact on the neonatal PK of the drug.
- For drugs that are known substrates of transporters, information gained from the conduct of pharmacokinetic studies in neonates can help elucidate the ontogenic trajectory of the transporter of interest.

5. *Clearance*

Plasma clearance is defined as the volume of plasma which is completely cleared of a drug in a given time period. Clearance as a function of age (PMA and PNA) in addition to weight are generally valuable parameters for determining the dose for each neonatal subgroup and can change rapidly based on the PNA.

- Clearance from target organs and tissues (e.g., brain) can also differ between neonates and older children and adults; therefore, compartment sampling (e.g., cerebrospinal fluid) to characterize the tissue exposure, when feasible, can be useful to determine the optimal dosing.
- As the clearance of a drug can be substantially different in various neonatal subgroups based on both PMA and PNA, it may be recommended to assess the clearance of a drug in each subgroup being studied.

6. *Additional Factors*

As increasing scientific data are garnered related to the prenatal and postnatal ontogeny of organs and tissues for ADME parameters in each of the neonatal subgroups, this information could be used to generate quantitative models such as PBPK to help design subsequent dosing strategies in those subgroups.²⁷

B. PD

Sponsors should collect and analyze both pharmacokinetic and, whenever possible, pharmacodynamic data in neonatal studies to determine how the two are linked with respect to exposure-response (E-R). PD could include the effect of the drug on biomarkers or clinical endpoints for both safety and efficacy. These measurements can help to determine if the E-R relationship of the drug in neonates is similar to that observed in older children and adults. If the relevant clinical endpoints cannot be measured directly, then an appropriate biomarker, if available, can be considered. As drugs given to neonates can affect multiple organ systems, it could be recommended to evaluate several biomarkers. In neonates, the ontogeny of the tissues and organs that are targeted by the drug can be critically important in predicting the potential

²⁷ See the FDA guidance entitled *Physiologically Based Pharmacokinetic Analyses — Format and Content* (August 2018).

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degree of response, thus altering the E-R relationships. These data are integral to any consideration of extrapolating efficacy data from studies in adults or other pediatric age groups.

Before conducting a clinical pharmacology study in neonates, all prior information should be considered. E-R relationships of the drug in adults and other pediatric age groups can help inform the neonatal studies. A poor or incomplete understanding of the natural history and pathophysiologic mechanisms of many neonatal conditions hinders the identification of clinically relevant pharmacodynamic biomarkers. Therefore, sponsors should initiate discussions early with the FDA when considering the use of novel biomarkers of response in neonatal studies.

C. Pharmacogenomics

Genetic differences that affect both the exposure of and response to a drug are increasingly documented, but the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in the neonatal population. Therefore, consider the following, if feasible:

- If there are pharmacogenetic differences that affect the PK, efficacy, or safety of a drug in older children and adults, pharmacogenetic analysis is recommended in neonates.

D. Immunogenicity

Immunogenicity to certain products (e.g., therapeutic proteins, peptides, oligonucleotides) can negatively impact the PK, PD, safety, and/or efficacy of the drug. The immune response in the neonatal period can differ from that of adults or older children; furthermore, how these differences affect the immunogenicity risk is not fully understood. Therefore, the immunogenicity of a drug should be assessed in neonatal trials regardless of the knowledge gained in adults and older children.

V. NEONATAL STUDY PLANNING

The following sections describe considerations for specific trial design elements when developing a neonatal study plan. Study planning should consider the ethics and the studies or approaches that would provide substantial evidence of effectiveness.

A. Approaches to Neonatal Studies

There are several approaches to providing substantial evidence of effectiveness for drugs for the pediatric population. In some cases, existing data in adults and other pediatric populations can be leveraged to provide this substantial evidence of effectiveness. This concept is often referred to as pediatric extrapolation.²⁸

²⁸ For more information, see the FDA draft guidances entitled *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) and *General Clinical Pharmacology Considerations for*

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Considering the distinct disease processes seen in the neonatal population, it is expected that pediatric extrapolation of effectiveness from other populations (e.g., adults, older children) would be infrequently possible. Most drugs developed for an indication specific to neonates will require at least one adequate and well-controlled study to establish substantial evidence of effectiveness. Regardless of the approach used to provide evidence of effectiveness, safety data should be obtained for all drugs studied in neonates. The magnitude of the safety database that should be obtained is determined by several factors, including for example, experience with similar drugs in populations of older children, adults, and neonates, the seriousness of the adverse reactions in the adult or pediatric populations, the rarity of the condition, and the potential for unique susceptibility to particular adverse events.

B. Ethics

It is recommended that an IRB reviewing neonatal research have specific expertise in neonatal trials.²⁹ Furthermore, it may be appropriate to utilize an independent Data and Safety Monitoring Board (DSMB) to oversee the neonatal trials; in such cases, the DSMB should also have expertise with neonatal trials.

VI. STUDY DESIGN CONSIDERATIONS

Intensive blood sampling for pharmacokinetic studies can rarely be undertaken in neonates because of their limited circulating blood volume. Furthermore, variability in the study population (e.g., a population undergoing rapid and varying rates of maturation) makes collection of clinical pharmacology information (e.g., PK, PD) uniquely challenging. Hence, it is important to use all available information and innovative approaches when designing a neonatal pharmacokinetic study. Modeling and simulation and pharmacologic considerations are often critical for the successful completion of a study. Some approaches that can inform the design and dose selection of neonatal studies include population PK, PBPK modeling, and/or pharmacokinetic/pharmacodynamic modeling approaches.³⁰ However, relevant ontogenic data with respect to ADME should be available before robust and accurate models can be developed for use in neonatal clinical studies.

The following sections describe considerations for specific trial design elements.

Pediatric Studies for Drugs and Biological Products (December 2014). When final, these guidances will represent the Agency's current thinking on this topic.

²⁹ Ethical considerations for pediatric studies and the role of the Institutional Review Board (IRB) in clinical trials involving pediatric participants are discussed in the FDA draft guidance *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the Agency's current thinking on this topic. See also 21 CFR part 50, subpart D.

³⁰ See the following FDA guidances: (1) *Physiologically Based Pharmacokinetic Analyses — Format and Content* (August 2018); (2) *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003); and (3) *Population Pharmacokinetics* (February 2022).

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A. Study Population

When conducting clinical pharmacology studies in neonates, the population enrolled should involve neonates that have the condition of interest or, in some cases, neonates who might be at risk for the condition of interest.

To account for variability in age and development, the sponsor should include as wide a spectrum of PMA and PNA in neonates as appropriate to cover neonatal subgroups for which the indication to be studied is relevant (see section III. Definition and Subgroup Classifications). When including a wide spectrum of neonates, the sponsor should plan for subgroup analyses (see section VI.G. Data Analysis).³¹

B. Dose Selection

Selection of an appropriate dose range to be studied is critical in deriving rational dosing recommendations for the neonatal population. Sponsors should use all existing pharmacokinetic and pharmacodynamic data (from adults, older pediatric populations, etc.) to help determine an initial dose in neonates. Clinical trial simulations that integrate PK, PD, biomarkers, and disease progression can help make this initial determination. Dose selection in neonates should also consider the PMA and PNA.³²

The rapid changes in growth and development occurring in neonates can require dosing adjustments over short periods of time (e.g., in certain instances, the initial dosing of anti-infective agents changes after 24 hours). Depending on the range of PNAs and PMAs being studied and the intended study duration, dosing regimens could become even more complex. Often, significant uncertainty about the dose in neonates necessitates alternative approaches that could involve titration of the dose, adaptive trial designs, or the use of therapeutic drug monitoring (TDM) during the trial. TDM can be particularly useful when there is known drug toxicity, or higher exposures are expected in neonates.

Given the unique ADME characteristics in neonates, different dosing regimens should be studied to optimize the exposure in various neonatal subpopulations. Neonates could require higher drug exposures than those in older children and adults to achieve adequate clinical benefit; in such cases, additional safety data should be collected to support the use of higher doses in neonates.

Given the uniqueness of some neonatal conditions, it is possible that in certain circumstances first-in-human studies should be conducted in the neonatal population (e.g., the drug is developed specifically for the neonatal condition, and nonclinical data preclude the possibility of studying the drug in healthy adult volunteers). In a first-in-human scenario (e.g., the target

³¹ Sponsors should be aware that individual jurisdictions may have differing privacy regulations regarding the collection of some of the information to assess PMA and PNA (e.g., precise birth date).

³² For additional information regarding dose selection, see the FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the FDA's current thinking on this topic.

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population is the neonatal population only), where sufficient data from adults or older children are lacking, sponsors should initiate discussions early with the FDA to determine potential approaches to dose selection.

C. Formulation

Proposed trials in the neonatal population should use an age-appropriate formulation. Neonates could present unique challenges associated with formulations and dosing. All aspects of the formulation, including the salt forms of the active ingredient, the excipients, and the volume of the unit dose, should be considered. Consideration should be given to the total volume for parenteral formulations to be administered, as the total intake volume may be limited and should also take into account the volume already received through parenteral nutrition and other standard-of-care drugs. Formulations should be developed to permit accurate dosing, especially given the potentially small unit doses. Studies of drugs in neonates should account for and capture information on potential interactions with tubing used for both parenteral and enteral administration and any potential interactions with co-administered fluids (including parenteral nutrition), enteral nutrition, and other therapeutic products.

The route of administration is important in neonates, given that many neonates are critically ill and unable to receive enteral products. While most products are developed for parenteral administration, other routes (e.g., enteral, inhalational, intraocular, transcutaneous, intramuscular, subcutaneous, rectal) can be considered when appropriate, depending on the condition and the clinical status of the neonate. The bioavailability of any non-parenteral formulation used in neonatal studies should be characterized in relation to the formulation used in older children and adults. Typically, bioavailability studies of age-appropriate formulations are conducted in adults; however, the potential for developmental differences in absorption between neonates and adults should be considered for dosing.

Considerations for excipients are particularly important in the neonatal population. The accumulation of excipients can be significantly higher in neonates because of immature organ function. In general, the sponsor should minimize the use of excipients in neonatal formulations whenever possible. Excipients with known toxicity in neonates should not be used (e.g., ethanol, propylene glycol, benzyl alcohol).

D. Sample Size

Sponsors should consider the number of neonates in various subpopulations to establish accurate dosing. Justification should be provided for the sample size selected. The precision of pharmacokinetic and pharmacodynamic parameters in the sample size calculation is critical for neonatal studies.³³ For example, one approach is to prospectively target a 95 percent confidence interval within 60 percent and 140 percent of the geometric mean estimates of clearance and

³³ For more information, see the FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the Agency's current thinking on this topic.

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volume of distribution for the drug in each pediatric stratum with at least 80 percent power.³⁴ Prior knowledge of the disease, drug exposure, and pharmacodynamic response from older children and adult data can be used to estimate the sample size for neonatal studies. The sponsor should account for sources of variability, including inter- and intra-subject variability, differences between neonatal subgroups, and differences between neonates and older children and adults in the final selection of the sample size for each neonatal subgroup.

Given the challenges associated with conducting studies in neonates, alternative and innovative approaches to traditional sample size requirements may be appropriate if they improve the interpretability of trial results. Clinical trial simulations that integrate pharmacokinetic and pharmacodynamic aspects can aid in the design the clinical pharmacology trials with feasible sample sizes. Practical considerations should be taken into account when determining the sample size if it is not possible to recruit adequate numbers of participants to achieve the desired precision of parameter estimates. The study sample sizes for neonatal subgroups should be discussed with the Agency prior to conducting the clinical pharmacology study.

E. Sampling

More often than not, blood samples are the primary samples collected in neonatal studies. Other types of samples, such as cerebrospinal fluid, urine, or saliva can be informative but are not as readily collected for the characterization of PK and PD.

1. Considerations for Blood Sample Volume Limits

Blood sample volumes for research studies should be limited to the least possible volume required for testing to minimize risk to the neonate. The sponsor should account for blood drawn for the study in addition to blood drawn for routine clinical assessments. If possible, blood samples for research studies should be timed with clinically indicated blood draws to minimize the blood volume and decrease the number of needle sticks or draws from an indwelling catheter.^{35,36} In some situations, it may be possible to improve the feasibility of pharmacokinetic studies by using blood from scavenged samples (i.e., samples obtained from surplus blood drawn during clinical care).

Greater consideration should be given for infants where illnesses specifically impact the ability to replace hemoglobin. It is important to know how slowly red cells will be replenished in the hospitalized neonate (which reflects GA, PNA, and the severity and type of illness) when determining the number of samples and sample volumes for the purposes of the study. In

³⁴ For more information, see the FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the Agency's current thinking on this topic.

³⁵ Howie SRC, 2011, Blood Sample Volumes in Child Health Research: Review of Safe Limits, Bulletin of the World Health Organization, 89:45-53.

³⁶ Veal GJ, 2014, Blood Volumes in Pediatric Clinical Trials: A Review of Current Regulations and Guidance for Research Studies, Clin. Invest, 4:1005-1011.

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general, neonatal blood volumes are approximately 85 mL/kg, increasing to 105 mL/kg by the end of the first month.^{37,38,39} Several studies have looked at the association between blood draws and the potential negative impact on neonatal blood volume and hemoglobin levels, including the need for transfusion in some instances.^{40,41,42}

Several academic centers and IRBs have published guidelines for total blood volume (TBV) limits for neonatal studies (including blood draws for both research and clinical care purposes).⁴³ In general, these guidelines describe acceptable ranges between 1 to 5 percent of the TBV for a single draw or over a 24-hour period and 3 to 10 percent of the TBV over a month. The sponsor should consider the amount of blood drawn for clinical purposes and the clinical status of the neonate. In addition, a minimum hemoglobin should be set before a research blood draw. Literature data on minimum hemoglobin values in neonates are limited. However, some institutions have minimum values, for example 7.0 g/dL for a stable neonate and 9.0 to 10 g/dL for a neonate with respiratory or cardiovascular compromise.⁴⁴ These values would be dependent on the PMA and PNA of the neonates in the study.

When planning a neonatal pharmacokinetic and/or pharmacodynamic study, sponsors should justify their proposed sampling scheme and the number of samples to be collected per neonate, considering PMA and PNA.

2. Sampling Schemes

Given the blood volume considerations for neonates, sparse sampling is a practical approach for obtaining pharmacokinetic data in neonatal studies. To effectively inform sparse sampling in neonates, it is essential to leverage what is known about the ontogeny of relevant organ and

³⁷ Guidelines for Blood Volumes in Clinical Trials (Especially in Pediatric Clinical Trials): <http://onbiostatistics.blogspot.com/2011/02/guidelines-for-blood-volumes-in.html>.

³⁸ Howie, S, 2011, Blood Sample Volumes in Child Health Research: Review of Safe Limits, Bull World Health Organ, 89(1):46-53.

³⁹ Pearson H, 2003, Blood and Blood Forming Tissues, Rudolph's Pediatrics, 21st ed, New York:McGraw-Hill, 1521.

⁴⁰ Madsen LP, MK Rasmussen, LL Bjerregaard, SB Nøhr, and F Ebbesen, 2000, Impact of Blood Sampling in Very Preterm Infants, Scand J Clin Lab Invest, 60:125-32.

⁴¹ Hack KE, CM Khodabux, JS von Lindern, HA Brouwers, SA Scherjon, HJ van Rijn, JA van Hilten, A Brand, and GC Page-Christiaens, 2008, Need for Blood Transfusion in Premature Infants in 2 Dutch Perinatology Centres Particularly Determined by Blood Sampling for Diagnosis, Ned Tijdschr Geneesk, 152:1419-25.

⁴² Testa M, F Birocchi, P Carta, and V Fanos, 2006, Causes of Anaemia in Very Low Birth Weight Infants: Phlebotomy Losses are not the First Accused, Minerva Pediatr, 58:263-7.

⁴³ Howie, S, 2011, Blood Sample Volumes in Child Health Research: Review of Safe Limits, Bull World Health Organ, 89(1):46-53.

⁴⁴ Howie, S, 2011, Blood Sample Volumes in Child Health Research: Review of Safe Limits, Bull World Health Organ, 89(1):46-53.

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enzyme systems as well as pharmacokinetic information that could be available in adults or older children. The sampling scheme should allow for the characterization of the clinically relevant exposure metrics that inform dosing.

Clinical practicality and the least burdensome approaches for neonates should also be taken into account when determining a feasible sampling scheme. In some situations, it may be possible to increase PK study feasibility by using opportunistic sampling (i.e., sampling around the time of clinically indicated blood draws) and scavenged samples for pharmacokinetic sampling and characterization.

When using opportunistic or scavenged samples, storage conditions should ensure sample stability, given that these samples are not generally collected with the primary intention of characterizing PK, and the approach to their collection and handling can differ from traditional pharmacokinetic samples. Careful, prospective planning is required when using an opportunistic approach and scavenged sampling, as there is less control of the sampling time with respect to the dosing time of the drug of interest and other concomitant medications. Lack of planning could increase the possibility that pharmacokinetic samples over critical periods of the dosing interval will not be collected, potentially making the information obtained unreliable.

The protocol should specify a standardized collection scheme, storage and handling conditions, accurate recording of the sampling times, the dose, and the dosing time of the drug of interest as well as any concomitant medications. The sponsor should assess the correlation between scavenged sample concentrations and prospectively collected pharmacokinetic sample concentrations to understand the extent to which drug concentration measurements are affected.⁴⁵ The acceptability of this approach depends on the quality and quantity of samples, the number of subjects, the total number of samples, and the variability of the data. When planning to employ such approaches, sponsors should consult with the FDA.

3. Sample Collection Methods

Sampling technique is critical including when using an available neonatal indwelling intravenous or intra-arterial catheter. Any sampling plan should also take into consideration the use of umbilical catheters and small caliber vascular access devices. If possible, pharmacokinetic samples should be obtained from a separate site other than that used for the administration of the drug product. Blood samples are generally collected and analyzed for drug concentrations via direct puncture to a vein from venous blood. While it is ideal to collect blood samples for analysis from the circulating blood volume, capillary or arterial sampling such as heel sticks can be used in the neonatal population if acceptable from a bioanalytical perspective.

When possible, opportunistic sampling or scavenging of biological fluids that are already being collected as part of routine clinical care such as cerebrospinal fluid or bronchial fluid, can provide additional pharmacokinetic information. For example, cerebrospinal fluid collected for clinical purposes can add to the understanding of the PK of the drug. However, proper collection

⁴⁵ Autmizguine J, DK Benjamin Jr, PB Smith, M Sampson, P Ovetchkine, M Cohen-Wolkowicz, and KM Watt, 2014, Pharmacokinetic Studies in Infants Using Minimal-Risk Study Designs, *Curr Clin Pharmacol*, 9(4):350-358.

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and storage of the sample as well as recording the time the sample was collected relative to the administration of the drug are critical to obtaining interpretable data. Urine and saliva collection could be considered, but the interpretation of data from such samples is also complicated and requires careful consideration before collecting. Non-invasive sampling using fluids can be useful if correlated with outcomes or blood or plasma drug levels. The volume of these samples in neonates can be small, and validation of the analysis in these small volumes should be provided.

From a feasibility perspective, dried matrix spots represent a potential methodology for acquiring biological samples.⁴⁶ Dried matrix samples consist of a collection of biological fluid on blotting paper and typically require low volumes. There are several dried matrix spot methods which can include dried blood spots (DBS), dried urine spots (DUS), and dried plasma spots (DPS). The most common dried matrix spot used in the neonatal population is DBS. Its minimally invasive sampling technique, the low blood volume required, and the ease of sample storage and handling are potential advantages of DBS. When using such an approach, bioanalytical validation should be conducted (see section VI.F. Bioanalytical Methods). If considering using such an approach, sponsors should initiate discussions with the FDA.

F. Bioanalytical Methods

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the drug and metabolites in the biologic fluids of interest is essential. Given the small volumes of study samples from neonates, sponsors should consider special assay techniques (e.g., ultra-low blood volume drug assays). These techniques should be validated so that these methods can be used with confidence in neonatal studies.⁴⁷

Standardized sample collection, and validated methods can reduce the number of limitations associated with the biomatrix. Before use in a neonatal pharmacokinetic assessment, the sponsor should account for any bias in concentration measurements of the microsampling methodology compared to those from a traditional sampling approach (e.g., plasma concentrations) that might have been used during the drug development in adults.

Sponsors are advised to obtain feedback from the relevant FDA review division early in the neonatal drug development process to determine the appropriate bioanalytical methods for the drug.

G. Data Analysis

There are two basic approaches for performing pharmacokinetic analyses in pediatric participants: (1) a standard non-compartmental pharmacokinetic approach; and (2) a population

⁴⁶ See the FDA guidance entitled *Bioanalytical Method Validation* (May 2018).

⁴⁷ See the FDA guidance entitled *Bioanalytical Method Validation* (May 2018).

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PK approach.⁴⁸ The population PK approach is more feasible in the neonatal population as it minimizes the total number of samples and hence the total volume of blood sampled per individual. Population PK approaches leverage prior information obtained from studies in adults and older children in conjunction with data collected from neonatal studies to provide estimates of the drug's pharmacokinetic parameters and their associated variability. However, any models that are developed for use in neonates should take into consideration all the ADME factors for each PMA and PNA subgroup and be supported by scientific data.^{49,50}

1. Application of Quantitative Approaches

The application of modeling and simulation (M&S) as a tool for dose selection in neonates should take into account the considerable variability in neonatal subgroups driven by differences in growth and maturation. In the absence of conducting a clinical trial in a large, diverse cohort of neonates, M&S can provide insights into dosing if such models are well informed, formulated, and executed. First, internal and external evaluations of the model should be performed to ensure that estimates of the drug's pharmacokinetic parameters are adequate and precise. Then, the model can be used to simulate dosing scenarios in the population for which the model was developed. Any trial design as a product of M&S should be flexible enough to mitigate the uncertainties inherent in the model outcomes. For example, in the commonly used sequential or staged study design, progressively younger cohorts are studied sequentially so that the trajectory of the dose-exposure or E-R relationships can be assessed. This conservative approach is widely used but can also significantly delay drug development in neonates, who are the youngest and most vulnerable age group. Alternative study designs (e.g., adaptive study designs) coupled with M&S can help streamline neonatal drug development.

2. Population PK

The population PK approach described in the FDA guidance entitled *Population Pharmacokinetics* (February 2022) has been the most commonly used approach in neonatal drug development studies. Population PK allows for the analyses of sparse (limited number of blood samples per individual) and unbalanced data (unequal distribution of blood samples in various

⁴⁸ For more information, see the FDA draft guidance for industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the Agency's current thinking on this topic.

⁴⁹ Kern, SE, 2009, Challenges in Conducting Clinical Trials in Children: Approaches for Improving Performance, *Expert Rev Clin Pharmacol*, 2(6):609-17.

⁵⁰ Rodieux, F, M Wilbaux, JN van den Anker, and M Pfister, 2015, Effect of Kidney Function on Drug Kinetics and Dosing in Neonates, Infants, and Children, *Clin Pharmacokinet*, 4(12):1183-204.

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parts of the concentration-time profile in the individuals). These factors are particularly important as both scenarios are typically present in neonatal studies.^{51,52}

3. PBPK Modeling

Another quantitative approach is PBPK modeling, a mechanistic modeling approach that incorporates the understanding of physiology and compound-specific information to predict the PK and/or PD of a drug.^{53,54} While PBPK prediction incorporates a more mechanistic understanding, its application in neonates is particularly challenging due to the limited understanding of rapid changes in neonatal physiology and the maturation of ADME processes in this population.

4. Covariates and Phenotype Data

In general, the following covariates for each neonate should be considered as part of data analysis: GA, birth weight, birth length, birth head circumference, PMA, PNA, current weight, body surface area (BSA), race or ethnicity, sex, diagnoses, concomitant and recent medications or intravenous fluids (including blood transfusions), type and amount of enteral feedings, and relevant laboratory tests that reflect the function of the organs responsible for drug metabolism and drug excretion. The sponsor should examine the relationships between the covariates and the PK of the drug of interest to assess the potential contribution of the covariates to the variability of pharmacokinetic parameters. Having enough subjects with or without the covariates of interest is important to determine the impact of these factors on the drug's PK. Also, the impact of pharmacogenetic factors could be critical to data analysis in some instances; therefore, sponsors are encouraged to collect DNA samples in neonatal pharmacokinetic studies when feasible.

A quantitative model can incorporate covariates to reflect the importance of individual characteristics (e.g., body size, PNA or PMA) or extrinsic factors (e.g., presence of concomitant medication) on pharmacokinetic parameters, resulting in more precise estimates of the PK of the drug on the next cohort.⁵⁵

⁵¹ Wang J, AN Edginton, D Avant, and GJ Burckart, 2015, Predicting Neonatal Pharmacokinetics from Prior Data Using Population Pharmacokinetic Modeling, *J Clin Pharmacol*, 55(10):1175-83.

⁵² Ku, LC and PB Smith, 2015, Dosing in Neonates: Special Considerations in Physiology and Trial Design, *Pediatr Res*, 77(1-1):2-9.

⁵³ See the FDA guidance entitled *Physiologically Based Pharmacokinetic Analyses — Format and Content* (August 2018).

⁵⁴ Maharaj, AR and AN Edginton, 2014, Physiologically Based Pharmacokinetic Modeling and Simulation in Pediatric Drug Development, *CPT Pharmacometrics Syst Pharmacol*, 3(11):1-13.

⁵⁵ Wang J, AN Edginton, and G Burckart, 2015, Using Modeling and Simulation for Neonatal Drug Development, *NeoReviews*, 16(11):e648-52.

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H. Clinical Study Report

In addition to other clinical pharmacology information, it is important to capture safety data in all clinical pharmacology studies of neonates. Classification of adverse events in neonates can be difficult given concomitant illnesses and medications.⁵⁶ Any potential adverse events related to drug administration should be documented in the clinical study report.⁵⁷

⁵⁶ Salaets, T, MA Turner, M Short, RM Ward, I Hokuto, RL Ariagno, A Klein, S Beaman, K Wade, M Thomson, E Roberts, J Harrison, T Quinn, G Baer, J Davis, K Allegaert, International Neonatal Consortium, Development of a Neonatal Adverse Event Severity Scale Through a Delphi Consensus Approach, *Arch Dis Child*, 104(12):1167-1173.

⁵⁷ For more information, see the FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014), which describes the elements of the Clinical Study Report for neonatal studies. When final, this guidance will represent the Agency's current thinking on this topic.