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

Final Guidance for Industry

What Is Covered in This Guidance?
This final guidance addresses the clinical pharmacology considerations for any planned studies in neonates submitted in new drug applications (NDAs), biologics license applications (BLAs), and supplements.

Why Is This Guidance Important?
- Neonates present unique absorption, distribution, metabolism, and excretion (ADME) characteristics.
- Many drugs administered in neonatal intensive care units (NICUs) are used in an off-label capacity.
- Pharmacokinetics (PK) and pharmacodynamics (PD) are affected by multiple factors in the neonatal population (e.g., size, growth and physiologic maturation, underlying illnesses, and concomitant medications) and may differ between neonates and older children and adults.
- Pharmacogenomics has not been extensively studied in the neonatal population.

What Is the Age Range for Neonates?
This guidance defines the neonatal period 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 through the expected date of delivery plus 27 days. When designing studies, it is important to consider stratifying the neonatal population to decrease variability. While neonates can be grouped by gestational age and/or weight at birth, postnatal age is another important variable to consider for stratification, as it can significantly affect ADME.
Prior to Neonatal Study Initiation:
Sponsors should assess the available scientific information regarding the neonatal condition, mechanism of action, PK, PD, and the ontogeny of any organs and tissues that are involved in the predicted response to the drug and or its metabolites.

Neonatal Study Design Considerations

STUDY POPULATION

DOSE SELECTION

SAFETY AND EFFECTIVENESS

The neonates enrolled should have (or in some cases be at risk for) the disease or condition of interest. It may also be necessary to enroll a wide spectrum of developmental age subgroups.

Dose range selection is critical for deriving rational dosing recommendations for the neonatal population. All existing PK and PD data, including from other populations, should be used to help determine an initial dose.

Regardless of the approach used to provide evidence of effectiveness, safety data should be obtained for all drugs studied in neonates.

An age-appropriate dosage formulation is required for neonates. Sponsors should consider the potentially small unit doses and ensure accurate dosing.

ETHICS

The 2014 FDA draft guidance on general clinical pharmacology considerations for pediatric studies recommends that an institutional review board reviewing neonatal research have specific expertise in neonatal trials.

In addition to clinical pharmacology information, it is important to capture safety data in all the clinical study reporting for neonatal studies.

Clinicians should consider all ADME factors for subgroups and be supported by additional scientific data.

Consider the necessary number of neonates in various subpopulations to establish accurate dosing and provide justification for the sample size selected. The precision of PK and PD parameters in the sample size calculation is critical.

CLINICAL STUDY REPORT

Two recommended approaches are: (1) standard noncompartmental PK and (2) PopPK. Neonatal models should consider all ADME factors for subgroups and be supported by additional scientific data.

BIOANALYTICAL METHODS

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the parent drug and metabolites in the biologic fluids of interest is essential.

SAMPLING

Use the smallest possible blood sample volume to minimize risk to the patient. It is essential to use all available information on the ontogeny of relevant organ and enzyme systems, as well as PK data, including from other populations.

DATA ANALYSIS

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the parent drug and metabolites in the biologic fluids of interest is essential.

SAMPLE SIZE

Consider the necessary number of neonates in various subpopulations to establish accurate dosing and provide justification for the sample size selected. The precision of PK and PD parameters in the sample size calculation is critical.

FORMULATION

An age-appropriate dosage formulation is required for neonates. Sponsors should consider the potentially small unit doses and ensure accurate dosing.

SAMPLE SIZE

Guidance Snapshots are a communication tool and are not a substitute for the guidance document.
To learn more about general clinical pharmacology considerations for neonatal studies, read the guidance: https://www.fda.gov/media/129532/download

1 Please see the 2014 FDA draft guidance titled General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products that can be accessed at the following link: https://www.fda.gov/media/90358/download
Background About the Guidance

This guidance supplements the FDA draft guidance titled General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (December 2014). The agency issued this guidance as part of an ongoing effort to support sponsors and investigators who are planning neonatal trials. Currently, many drugs are used off-label in NICUs, and there have been cases where adult drugs have been ineffective or even harmful to neonates. The FDA would like to spread the message that therapies designed specifically for neonates need to be developed, and neonates can be protected through inclusion in clinical research.

Guidance Recommendations Apply Throughout the Drug Development Timeline

This guidance provides recommendations for neonatal clinical pharmacology studies. Before initiating neonatal clinical pharmacology studies, the sponsor should assess the available scientific information regarding the mechanism of action and PK of the drug, as well as 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 guidance does not discuss the timing to initiate neonatal studies. Sponsors should direct questions on the initiation of neonatal studies with the relevant FDA review division.

Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

Speakers: Elimika Pfuma Fletcher, PhD, policy lead for the Office of Clinical Pharmacology, Gerri Baer, MD, team lead for pharmacovigilance and neonatology in the FDA’s Office of Pediatric Therapeutics (OPT)

To learn more about the general clinical pharmacology considerations for neonatal studies for drugs and biological products, read the guidance: [https://www.fda.gov/media/129532/download](https://www.fda.gov/media/129532/download)

To see additional Guidance Snapshots, check out the pilot program: [https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot](https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot)