Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development

Guidance for Industry

DRAFT GUIDANCE

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[February 2023]
[Clinical/Medical]

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Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development: Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide a framework for considering whether and what type of long-term neurologic, sensory and developmental evaluations could be useful to support a determination of *safety* of a drug, biological product, or device (referred to as 'medical product' in this guidance) for use in neonates[2], and if so, which domains of neurodevelopment may be most applicable.

This guidance will not specifically address *efficacy* or *effectiveness* assessments for products primarily intended to improve neurologic outcomes, e.g., neuroprotective agents. This guidance is focused on long-term evaluations of neurodevelopmental safety. Although assessments of nephrotoxicity, pulmonary toxicity, and toxicity to other tissues and organs may also be warranted in neonatal medical product development, the approach to those assessments is outside the scope of this guidance.

Pertinent information on planning clinical pharmacology studies in neonates[3] and pediatric patients[4] can be found in existing guidance documents.[5] This guidance does not focus on nonclinical safety studies to support clinical studies in neonates, nor does it address clinical study

[1] This guidance has been prepared by the Food and Drug Administration: Office of Pediatric Therapeutics in the Office of the Commissioner; the Division of Pediatric and Maternal Health, the Division of Antivirals, the Office of Surveillance and Epidemiology, and the Office of Neuroscience in the Center for Drug Evaluation and Research;, the Center for Biologics Evaluation and Review; and the Center for Devices and Radiological Health.

[2] The neonatal period is defined in the *Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11 (R1)* (2017) as including term, post-term, and preterm newborn infants. The neonatal period for term and post-term infants is the day of birth plus 27 days. For preterm infants, the neonatal period is defined as the day of birth through the expected age of delivery plus 27 days. These same definitions will apply for purposes of this guidance.

[3] See the FDA Guidance for Industry, *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products*; July 2022.

[4] See the FDA Draft Guidance for Industry, *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products*; September 2022. When finalized, this guidance will represent the Agency's current thinking.

[5] FDA updates 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.

design in neonatology. This guidance also does not address neonatal or pediatric safety assessments following studies conducted during pregnancy.[6]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances 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). FDASIA contained several provisions to encourage medical product development in neonates.[7]

Treatment with medical products during the neonatal period coincides with a time of critical growth and physiologic development. Short-term safety evaluations typical for adults or other populations may fail to identify important adverse effects in the neonatal population, as latent effects may follow early-life exposures. Historically, most medical products used to treat neonates and young infants were not approved for use in this population for the relevant indications, and thus, long-term effects were rarely systematically evaluated.

Clinical investigators and sponsors[8] of neonatal studies should consider and assess potential short-term and long-term effects of an investigational therapy, whether the therapy is novel or previously developed for a different indication or population. Short-term clinical improvement, such as that observed after high-dose corticosteroids for infants with bronchopulmonary dysplasia, may be followed by unexpected long-term harm.[9] While adjunctive neurological assessments (e.g., neuroimaging, electroencephalography) may provide information on early safety concerns, they cannot replace clinical assessments of long-term functional outcomes. Although there is no universal definition of "long-term," for the purpose of this guidance, the time frame can be generally thought of as at least 2 years of age or at such time when relevant clinical neurodevelopmental parameters can be reasonably assessed (refer to sections IIIB2a and IIIC1). Prospectively designed long-term follow-up is often important to understand medical product safety in neonates.

Neonates should have access to medical products adequately evaluated for dosing, efficacy or effectiveness, and/or safety for that population. There are conditions unique to term or preterm

[6] For additional information, see the FDA Draft Guidance for Industry, *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Studies*; April 2018. When finalized, this guidance will represent the Agency's current thinking.

[7] 8 Title V Sec 501(a) of FDASIA can be found at https://www.congress.gov/112/plaws/publ144/PLAW112publ144.pdf.

[8] For the purposes of this guidance, "sponsor" refers to commercial sponsors and academic investigators who may plan and carry out neonatal clinical studies.

[9] Committee on Fetus and Newborn. Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. *Pediatrics*. 2010;126:800-808.

neonates, such as necrotizing enterocolitis and retinopathy of prematurity, that will not have analogous development programs in older populations. As new medical products are developed for these and other unique neonatal conditions, novel development programs and first-in-human studies may be initiated in neonates, and these development programs should also demonstrate long-term neurologic, sensory, and developmental safety. Neonates should also be enrolled in clinical studies for medical products and diagnostic tools initially developed for indications in other populations that will be used for neonates. Inclusion of neonates in such studies may be useful to establish dosing, safety, and efficacy or effectiveness, and these studies may also warrant long-term safety evaluations.

III. NEURODEVELOPMENTAL FOLLOW-UP FOR PRODUCT DEVELOPMENT PROGRAMS THAT INCLUDE NEONATES

Long-term neurodevelopmental safety should be considered as part of neonatal product development plans. Sponsors should communicate as early as possible with the relevant FDA review division to reach alignment on the appropriate approach for long-term safety evaluations.

A. Determining the Need for Long-term Neurodevelopmental Safety Evaluations

Sponsors should assess whether a long-term neurodevelopmental safety evaluation for neonates enrolled in clinical studies should be conducted. This assessment should be initiated early in product development and should be reevaluated as new information becomes available.

1. General Considerations

a. Systemic Exposure: Any route of administration may result in a systemic exposure. The degree of systemic exposure, which should be quantified in early pharmacokinetic or animal studies if possible, may inform the need for long-term safety assessment. In general, higher levels of systemic exposure may be associated with higher central nervous system (CNS) exposure and potential risk for long-term sequelae.
b. Timing of Exposure: The timing of exposure to a drug, biological product, or device relative to a particularly vulnerable stage of organ and tissue development may inform the need for and the type of long-term safety assessment.
c. Duration of Exposure: Repeated dosing, repeated treatment, prolonged exposure and medical products with persistent effects may be associated with higher risk for long-term sequelae; however, long-term safety assessments may also be required after single doses or treatment, short durations of investigational therapies, based on the other considerations described in this guidance.

2. Patient and Population-specific Considerations

a. Neurodevelopmental vulnerability: The anticipated rates of developmental, behavioral, and sensory impairments are inversely related to gestational age

and birth weight and differ significantly across various congenital or acquired conditions. Sponsors should seek the most current data to understand background rates of specific long-term neurodevelopmental outcomes in the population of interest.

b. Disease state characteristics: The disease or pathophysiology of the condition under study (e.g., metabolic processes or conditions associated with compromised blood-brain barrier integrity or altered cerebral blood flow such as meningitis, hypoxic-ischemic encephalopathy or perinatal arterial ischemic stroke) may increase the risk for adverse neurodevelopmental outcomes. Sponsors should address disease-specific vulnerabilities in the proposed evaluation of neurodevelopmental safety.

3. Product-specific Considerations

a. Nonclinical toxicity: Nonclinical studies conducted to specifically evaluate the potential adverse effects of an investigational medical product on the developing CNS of neonates and young infants should include pre- and postnatal development studies, and, if warranted, embryo-fetal development and/or dedicated juvenile animal studies testing the investigational medical product in very young animals at critical and comparable stages of brain development.[10] These studies can test both the intended effects of an investigational product and also can identify unintended or off-target effects. These data can and should be used to inform risk assessments for neonates and young infants and can also inform the design of clinical studies (e.g., inclusion of specific endpoints, identification of potential windows of developmental vulnerability). However, because CNS development and maturation are extremely complex, extrapolation across species development is challenging. Nonclinical studies cannot test all potential neurological effects of a medical product, and the lack of adverse effects in nonclinical studies alone does not necessarily exclude the possibility of adverse effects in neonates.

b. Clinical pharmacology: The mechanism of action, target organ or tissue, disposition and tissue distribution of the product, and/or accumulation of metabolites (and ontogeny of these factors) may evoke concerns about long-term neurodevelopmental safety. For example, drugs and biological products thought to penetrate the CNS are likely to warrant long-term safety assessment in neonates. Exposures may also be affected by developmental changes in the activity of drug metabolizing enzymes and the ontogeny of renal function in the neonatal period.[11]

c. Clinical experience: Data from use of a drug or device in other populations may be incorporated into the discussion about potential toxicities and need for follow-up after neonatal studies. Neurologic safety signals identified in older pediatric and adult patients should be carefully evaluated in neonates. It is

[10] See the ICH Guidance for Industry, *S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals*; May 2021.

[11] See the FDA Guidance for Industry, *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products*; July 2022.

important to note that the absence of a safety signal in older populations may not preclude adverse effects in neonates. Novel medical products developed for conditions that occur only in neonates may not have available safety data from other populations and a comprehensive neurodevelopmental safety evaluation may be useful in these situations (see section III.C.3).

d. Product components: Both the active pharmaceutical ingredient and all excipients (e.g., ethyl alcohol and benzyl alcohol) and impurities (e.g., heavy metals and trace elements) should be considered when assessing the potential of a drug to cause neurodevelopmental toxicity. For devices that directly or indirectly contact human tissues, a biocompatibility evaluation should be conducted to assess for the potential for adverse responses resulting from contact of the component materials with the body.[12]

B. Factors to Consider When Developing a Plan to Evaluate Long-term Neurodevelopmental Safety

If after conducting the assessment described in section IIIA, a sponsor determines that a long-term neurodevelopmental safety evaluation should be conducted, the sponsor should justify and design such an evaluation based on sound scientific rationale. A controlled study design is recommended, whenever feasible. Although a single-arm study may be useful for collecting some types of safety information, the absence of a concurrent control arm (placebo or active comparator) will generally make clear interpretation of the results difficult, if not impossible. A control group allows for easier discrimination of drug or device-related patient outcomes from outcomes caused by other factors, including underlying disease and developmental progression, especially if the natural history of the condition in the patient population is not well-established.

1. General Considerations

a. Standardization: Sponsors should ensure reliability of administration and scoring of evaluations across sites and examiners, including consistency in the study instruments used and the age at follow-up.

b. Community acceptance and inclusivity: Development of a long-term safety study plan should include an assessment of family perceptions and early identification of barriers to study participation, including potential mistrust. Engagement of patient families and community leaders early in development and at the protocol development stage may help promote participation of historically underrepresented communities and improve overall study recruitment and retention.

c. Multidisciplinary input: Sponsors may identify and address challenges and opportunities in study development through engagement of key stakeholders. Stakeholders may include, but are not limited to, patients, parents, caregivers, health care providers, educators, and developmental specialists. These stakeholders are instrumental in identifying clinically

[12] See the FDA Guidance for Industry and Food and Drug Administration Staff*, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*"; Sept. 2020.

meaningful outcomes and assessing the acceptability and feasibility of the study design.

d. Patient recruitment and retention: Ideally, sponsors should include the long-term follow-up evaluation as a component of the initial study enrollment. Although this will not eliminate missing data, early recruitment will reinforce the importance of the long-term safety evaluation. Loss of patients over time threatens the integrity of long-term neurodevelopmental safety studies. There should be appropriate plans in place to keep families engaged and to collect relevant contact information (e.g., home and mobile phone numbers, email addresses, other messaging modalities) as needed to encourage retention of study participants and important data. Study participants may relocate during the follow-up period and maintaining contact is an important means to reduce the risk of missing patient information.

e. Patient burden: Sponsors developing long-term safety evaluations should consider and mitigate barriers to follow-up study enrollment as well as minimize the short-term and long-term burdens of study participation to the subjects and their family. Sponsors may consider and propose a strategy for integrating data from community-level services and providers involved in routine? neurodevelopmental evaluations and tracking (e.g., early intervention and Child Find programs) and pediatric evaluations during usual care (see maintaining data quality considerations below, *Section B.1.c*). Additional strategies may include use of mobile technology for information collection and transfer.

f. Data quality: While some information can be reasonably gathered through evaluations in usual clinical practice, general developmental screening performed during routine care is rarely a reliable substitute for a formal diagnostic neurodevelopmental evaluation. In addition, some neurodevelopmental evaluations require specialist evaluation. A sponsor may be able to rely on certain objective developmental measures with established reference standards (e.g., growth, vision, and hearing screening) captured during routine care where the sponsor can ensure they are collected reliably.

2. Patient/Population-specific Considerations

a. Timing and duration: For the evaluation of neurodevelopmental safety, outcomes should be evaluated up to at least 2 years of age, adjusted for prematurity,[13] if appropriate. The duration and frequency of follow-up assessments should be supported by scientific data and sound rationale. Considerations may include the static or dynamic nature of the neurodevelopmental outcome(s) being evaluated. The follow-up plan also should consider the ages at which the outcomes of interest can be

[13] Adjusted age, (also called "corrected age" or "post-menstrual age") is defined as the chronological age reduced by the number of weeks born before 40 weeks of gestation. Refs: AAP Committee on Fetus and Newborn. "Age terminology during the perinatal period;" *Pediatrics* 2004;114(5):1362-4 and *E11: Clinical Investigation of Medicinal Products in the Pediatric Population;* International Council for Harmonization, 2000.

reasonably measured. For example, some learning difficulties or neurologic disorders may not present or be reasonably discernable with available assessment tools until after 2 years adjusted age.

b. Related factors: Sponsors should consider how other factors that relate to and affect neurodevelopmental outcomes may influence the interpretability of study results and should collect relevant covariate data accordingly.
   i. Comorbidities (e.g., prematurity, congenital heart disease)
   ii. Socioeconomic factors (e.g., food insecurity, social stressors, parental education level)
   iii. Perinatal factors (e.g., substance use during pregnancy, depression)
   iv. Regional differences in health care systems and accepted standards of medical practice
   v. Environmental factors (e.g., lead or chemical exposure)
   vi. Intercurrent events (e.g., illness, injury, therapies [such as early intervention], and other medications)

c. Developmental domains: In most cases, a general assessment of all the key neurodevelopmental domains is recommended. (See Section C.3, below). If specific domains of vulnerability are known or suspected in the study population based on product characteristics, then sponsors should identify the existing validated, age-appropriate tools to carefully measure relevant outcomes within those domains.

d. Feasibility: There may be population or study-specific issues that affect the feasibility of planned long-term follow-up studies. Sponsors should assess feasibility early in drug or device development and provide study plans for Agency review. This may include alternate strategies (e.g., patient registries, observational studies) if needed.

3. Product-specific Considerations

a. Tissue specificity: Sponsors should determine whether the product has effects on organ systems that may impact neurodevelopment. Medical products may have direct and/or indirect effects on the developing CNS. Understanding these effects can help determine not only the extent of long-term follow-up but also the type of assessment needed.

b. Ontogeny of therapeutic target: Sponsors should determine whether a medical product's target changes in distribution or function throughout maturation. The extent of medical product exposure in relation to known target tissue developmental changes should be considered when designing the plan for neurodevelopmental safety evaluation.

C. What to Measure, When and For How Long?

The most useful type of neurodevelopmental safety evaluation will depend upon whether it is determined (based on considerations discussed in sections IIIA. and IIIB. above) that a comprehensive neurodevelopmental evaluation is appropriate and/or whether there are specific developmental domains of concern that warrant targeted evaluations (see section III.C.3). As sponsors are planning long-term neurodevelopmental evaluations, they

should consider what assessment tools to use, at what time point(s), and for how long. Neurodevelopmental safety evaluations should include validated tools, when available, to ensure rigor and should provide broad-ranging assessments of neurologic function, including relevant clinical outcome assessment (COA) tools. Note that general developmental screening and formalized assessments of neurodevelopment are not interchangeable.

1. Timing of Safety Evaluations

In general, outcomes should be evaluated at a minimum of 2 years adjusted age. Earlier and/or later evaluations also may be warranted.

a. Evaluations that can be reliably performed during the first 2 years (adjusted age) of life and require longitudinal monitoring, including head growth, hearing and vision testing, neurologic exam, and developmental milestones, provide important information and may be appropriate.
b. Comprehensive neurodevelopmental outcomes should be evaluated at a minimum at 2 years adjusted age.
c. Assessment of more subtle, but important cognitive, language, behavioral, and other outcomes may require children to be followed until later in childhood. Problems in these areas may not be clearly discernable or adequately assessed in the first 4–6 years of life. Depending on the specific domains of concern, longer follow-up may be useful even if there are no neurodevelopmental concerns observed at the initial 2-year assessment.

2. Key Characteristics of Measurement Tools

Long-term safety evaluations should be based on well-defined and reliable COAs. Specifically, COAs should assess clearly defined concepts of interest with appropriate justification to support their use in neonatal long-term safety evaluations.[14] Assessments should include those that measure how a subject is functioning in daily life. Key considerations relevant to long-term safety assessment after neonatal studies include:

a. Minimizing participant burden and avoiding duplication can increase pediatric patient testing compliance and reduce behavioral interference (e.g., refusal to participate in testing), which can confound or invalidate test scores. It can also reduce missing data and increase the feasibility for administration across large cohort studies.
b. Identifying and accounting for potential confounding factors that may compromise the validity of an assessment and score interpretability is important when devising a plan for analyzing test scores. For example, a cognitive assessment that depends on patients having typical fine motor

[14] See the Draft Guidance for Industry, Food and Drug Administration Staff and Other Stakeholders, *Patient-focused Drug Development: Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcome Assessments*; June 2022, for further discussion of these characteristics. When finalized, this guidance will represent the Agency's current thinking.

functioning (e.g., a time-limited block design task) may yield unreliable scores for children with fine motor impairments.

c. Carefully considering score selection within neurodevelopmental assessments, especially for patient populations that may be at the greatest risk of impairment, can help contextualize results if the selected COA has known limitations. Some scores (e.g., standardized scores) may demonstrate floor effects in severely impaired children and ceiling effects in children with developmentally advanced skills.
d. Selecting COAs that are methodologically sound with well-established psychometric properties is important, particularly to ensure validity across multicenter studies.
e. Ensuring that selected COAs have demonstrated reliability across the demographic groups included in the study, including availability in languages appropriate for global sites to support generalizability of study results. Consider, for example, that a language assessment developed for U.S. English speakers may yield unreliable, uninterpretable scores when used with patients at non-U.S. English speaking sites. Selected COAs should include robust norms for term and preterm infants.

3. Domains of Assessment

When a comprehensive neurodevelopmental evaluation is needed, it should also include evaluation of physical, mental, and social health. The assessment may include the following domains:

a. General
    i. Physical Health—including ongoing health conditions (e.g., seizure disorder, pulmonary conditions, renal impairment), feeding problems, somatic growth (height, weight, and head circumference)[15], sleep
    ii. Quality of life and global function in daily life
    iii. Receipt of developmental interventions and educational services
b. Neurodevelopment
    i. Sensory
    ii. Motor
    iii. Cognition[16]
    iv. Emotional and Behavioral Health
    v. Communication
    vi. Social Functioning
    vii. Adaptive Functioning

4. Relevant Covariates

[15] See the Draft Guidance, *Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials: Guidance for Industry* for information on measuring growth parameters. When finalized, this guidance will represent the Agency's current thinking.

[16] Cognition also includes executive function, attention, working memory, and processing speed.

Relevant covariates such as demographic variables and other factors that may change over time should be assessed longitudinally and systematic data collection of these factors should be incorporated into the proposed follow-up plan. (See Section IIIB2b.)

5. Adjunctive Assessments (i.e., Biomarkers of Neurodevelopmental Outcome)

In general, adjunctive assessments and biomarker measures may not provide as meaningful information as long-term functional outcomes assessments and may not substitute for the above evaluations. However, adjunctive assessments may be useful to support the evaluation of neurodevelopmental safety, especially when following a known signal of concern from nonclinical studies, studies in a different population, or known effects of medical products from a similar pharmacological or therapeutic class. Thus, how useful an adjunctive assessment could be is typically product-specific and should be discussed with the appropriate review division at the time of protocol development.

a. Neuroimaging studies may be used to assess anatomical evidence of toxicity (e.g., brain MRI to assess disruptions in myelination) but should typically have clinical correlation.
b. Neurophysiologic testing may also be used to evaluate a specific safety signal and may include (not a comprehensive list):
    i. Visual-evoked-response
    ii. Somatosensory evoked potentials to facilitate differentiation between peripheral and central nervous system insults
    iii. Auditory-evoked response
    iv. Electromyography with or without nerve-conduction studies
    v. Electroencephalography