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FDA prioritizes neurodevelopmental safety of medical products used in neonates

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Clinical trials to support Food and Drug Administration (FDA) approval of medical products used in neonates often are not long enough to capture latent effects on neurodevelopment. Therefore, the FDA is taking steps to ensure the long-term neurodevelopmental safety of products used in the neonatal period.

A product's potential adverse effects on a neonate's developing nervous system may not manifest clinically until well after exposure, once the child is older. For example, short-term clinical improvement has been observed with use of high-dose corticosteroids to treat chronic lung disease in preterm neonates. However, later studies have shown that this treatment may be associated with long-term

neuromotor impairment, according to the AAP policy statement *Postnatal Corticosteroids to Prevent or Treat Chronic Lung Disease Following Preterm Birth* (https://bit.ly/40ETVeI).

Among its efforts to ensure well-designed, well-executed controlled clinical trials are conducted to evaluate long-term neurodevelopmental safety of drugs, the FDA issued a postmarketing requirement for Sezaby (phenobarbital sodium). The drug was approved in 2022 for the treatment of neonatal seizures in term and preterm infants. The requirement specifies that the drug manufacturer needs to follow patients for a minimum of five years using validated, age-appropriate developmental assessments of motor skills, cognition, language and behavior.

“This is an important opportunity to comprehensively evaluate the long-term neurologic effects of a drug that has been used in clinical practice for decades,” said An Massaro, M.D., the FDA’s lead neonatologist in the Office of Pediatric Therapeutics.

To help facilitate planning for long-term studies, the FDA recently issued draft guidance that outlines factors companies should consider when studying a product in neonates (https://bit.ly/3AFneDa). Such factors include the extent of systemic exposure to the product (especially to the nervous system), the timing of exposure relative to a vulnerable stage of organ or tissue development and the duration of the exposure. The guidance also highlights various population and product characteristics that may increase the likelihood that long-term neurodevelopmental safety evaluations will be needed. The FDA will review comments received on the draft guidance before providing final guidance on this topic.

When determining the need for a long-term neurodevelopmental study of Sezaby, the FDA considered both population characteristics (e.g., the increased risk for adverse neurodevelopmental outcomes for neonates with conditions associated with neonatal seizures) and product characteristics (e.g., previous nonclinical and clinical studies that suggested potential neurodevelopmental safety concerns associated with phenobarbital use).

The FDA also participates in the International Neonatal Consortium, a global collaboration that seeks to forge a predictable regulatory path for evaluating the safety and effectiveness of medical products for neonates. The consortium has spearheaded many opportunities to improve and accelerate neonatal product development, including developing recommendations for examining long-term outcomes (Marlow N, et al. *Pediatr Res*. 2019;86:567-572).

The FDA's Office of Pediatric Therapeutics and Office of New Drug's Division of Pediatrics and Maternal Health and Division of Neurology II contributed to this article.

Resources

- FDA draft guidance on considerations for long-term clinical neurodevelopmental safety studies in neonatal product development
- Information on medical product development for neonates
- International Neonatal Consortium