June 7, 2023

The Honorable Robert M. Califf, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Dear Dr. Califf:

We, the undersigned organizations that represent diverse communities across the country, are writing to express our profound concern with recent FDA actions supporting drug products that unnecessarily expose babies to high levels of toxic aluminum. Our organizations are committed to improving the health and well-being of our nation's underserved populations. This includes our tiniest, most vulnerable patients—babies hospitalized in a neonatal intensive care unit ("NICU"). We urge the FDA to withdraw its draft guidance issued in December 2022 suggesting that the FDA may approve "total parenteral nutrition" (TPN) products with high levels of aluminum,[1] and rescind and prohibit approval of high aluminum products promptly to eliminate aluminum toxicity threat to the hundreds of thousands of preterm babies born each year.

Preterm Birth is a Significant Contributor to Racial Disparities in Infant Mortality

Each year, more than 380,000 babies in the United States are born prematurely (*i.e.*, at less than 37 weeks), representing a staggering 10.5% of all live births.[2] Of these, more than 50,000 are born very prematurely, *i.e.*, at less than 32 weeks.[3] Preterm-related issues are the leading cause of infant death in the United States, accounting for more than one-third of all such deaths.[4] Preterm babies that survive may suffer from developmental delays, hearing and vision impairment, and chronic respiratory disorders.[5] The annual societal economic cost associated with preterm birth in the United States is approximately $25 billion.[6] In addition, preterm birth rates are linked to significant racial and ethnic disparities in health outcomes in the United States. The preterm birth rate among Black women is 52% higher than the rate among all other women; approximately 14.2% of Black infants are born prematurely, compared to 11.6% of American Indian/Native Alaskan infants, 9.8% of Hispanic infants, and 9.2% of white infants.[7]

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[1] *See* FDA, *Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations—Draft Guidance for Industry* (Dec. 2022), *available at* https://www.fda.gov/media/163799/download.
[2] *See* March of Dimes, *A Profile of Prematurity in the United States*, https://bit.ly/42bZ137 (last visited May 1, 2023).
[3] *Id.*
[4] *Id.*
[5] *Id.*
[6] *Id.*
[7] *Id.*; *see also* March of Dimes, *2022 March of Dimes Report Card*, at 12, *available at* https://bit.ly/3NyH0bv (last visited May 1, 2023) (reporting similar numbers).

Aluminum Exposure is a Serious Toxicity Risk for Infants, Especially Those Who Are Born Prematurely

Because many preterm babies' digestive systems are not yet fully functional, they must obtain all their nutrients intravenously, *i.e.*, through TPN. Typically, a baby who requires TPN will be given a personalized mixture of amino acids, carbohydrates, lipids, electrolytes, vitamins, and minerals. Many of the drug products that are used for TPN are contaminated by trace amounts of aluminum. Because preterm babies' kidneys are not yet mature, they are not able to filter out the aluminum introduced through TPN products, which instead accumulates in their organs and bones.

While it is difficult to determine—and control—how much aluminum an infant is receiving through TPN, **any amount of avoidable aluminum in a TPN drug product is undesirable.** It creates serious risks and offers no clinical benefits. Decades of research has established that just a few days of excess aluminum exposure in the NICU can cause lasting toxicity in the brain, skeletal system, liver, and other areas of the body. [8] Any damage caused by excess aluminum exposure typically manifests itself only years later and may be difficult or impossible to reverse.

The FDA Has Long Recognized These Risks, But New Guidance Would Substantially Boost Allowable Amounts of Aluminum—Deepening Racial and Ethnic Inequality

The FDA has long recognized the risks for infants, especially those born prematurely, but the agency's approach to aluminum contamination has been inconsistent at best in recent years. In some cases, FDA has insisted that drug manufacturers dramatically reduce the aluminum content of TPN products to as low as possible. In other cases, however, FDA has allowed similar products to enter or remain on the market with staggeringly higher aluminum contamination.[9]

The FDA's recently issued draft guidance is a step in the wrong direction because it would boost the allowable amount of aluminum in some products by as much as 17 times more than before.[10] While the agency may value increasing drug competition, this should not jeopardize the health and safety of premature babies struggling for survival in the NICU. The racial and ethnic disparities currently impacting our communities will worsen.

The FDA Should Ensure Drug Manufacturers Reduce Aluminum Contamination to the Fullest Extent Possible

FDA should therefore adopt a consistent approach of requiring drug manufacturers to reduce aluminum contamination in TPN products to the fullest extent that existing technology will allow. It is not fair or reasonable, and is certainly inconsistent with the FDA's core mission of

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[8] *See, e.g.*, Aluminum Effects in Infants and Children (2019) *available at* https://publications.aap.org/pediatrics/article/144/6/e20193148/37901/Aluminum-Effects-in-Infants-and-Children?autologincheck=redirected

[9] *See, e.g.*, FDA, Infants at Risk for Aluminum Toxicity with Unapproved Potassium Phosphates Drug Product (Feb. 9, 2023), https://www.fda.gov/drugs/drug-safety-and-availability/infants-risk-aluminum-toxicity-unapproved-potassium-phosphates-drug-product.

[10] *See* FDA, *Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations—Draft Guidance for Industry* (Dec. 2022), *available at* https://www.fda.gov/media/163799/download.

safeguarding public health, to allow the marketing of products with unnecessarily high aluminum content. Such products simply pose too much risk to infants, even if they are labeled for adult patients only. FDA has extensive evidence for decades that products labeled for adult patients are used in pediatric patients. FDA does not control clinical practices and the parents of preterm babies are rarely if ever made aware of the extent of aluminum exposure and the resulting toxicity coming from TPN products. FDA is the best and final gate-keeper on drug safety and should exercise its authority fully and without exception in dealing with aluminum toxicity.

We therefore urge FDA to undertake a comprehensive review of its policy on aluminum contamination in TPN products as soon as possible, withdraw the 2022 draft guidance suggesting that FDA may approve TPN products with high levels of aluminum, adopt a formal policy that FDA will not grant or maintain approval of a high-aluminum TPN product that is unsafe to preterm babies when a lower-aluminum product is available, and remove such products from the market.

These actions are a necessary step to address pervasive health disparities impacting vulnerable and underserved populations across the country. We cannot afford to miss the opportunity to focus our attention on the very early days, i.e., in the NICU. Thank you for your consideration of this serious issue.

Sincerely,

ASPIRA Association

Center for Black Equity

CNC

Diversity Uplifts, Inc.

Health Equity Collaborative

MANA Action Fund

National Hispanic Medical Association

National Black Child Development Institute

Partnership for Innovation and Empowerment

SER National

Southern Christian Leadership-Global Policy Initiatives (SCL-GPI)

The Latino Coalition

United States Hispanic Leadership Institute