Memorandum

Date	October 20, 2023
From	(HFS-255) Through , Ph.D. (HFS-255) , Ph.D. (HFS-255)
Subject	Regulatory status of live microorganisms when used or intended for use in food for pre-term infants
To	Office of Compliance

This memorandum concerns the consumption of live microorganisms used or intended for use in food for pre-term infants. We are aware that products containing live microorganisms are being marketed in neonatal intensive care units (NICUs) in the United States.[1] In the U.S., while some infant formulas for term infants contain live microorganisms, formulas for pre-term infants do not.[2] CFSAN's Office of Compliance (OC) asked the Office of Food Additive Safety (OFAS)'s Division of Food Ingredients (DFI) whether live microorganisms, when used or intended for use in food for pre-term infants, render a product adulterated within the meaning of section 402(a)(2)(C)(i) because this use of live microorganisms is an unsafe food additive within the meaning of sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic (FD&C) Act.[3]

Any substance added or intended for addition to food must have premarket approval by FDA for that use unless the use is generally recognized as safe (GRAS) by qualified experts or meets one of the listed exceptions at section 201(s)(1)-(6) of the FD&C Act. Otherwise, the substance is deemed an unapproved/unsafe food additive, and food that is or contains an unapproved/unsafe food additive is adulterated under the FD&C Act. There is no food additive regulation that authorizes the use of any species of live microorganism as a food additive for

[1] Hanna et al. (2023) "Current patterns of probiotic use units: a multi-institution survey" American Journal of Perinatology.
[2] Poindexter (2021) "Use of probiotics in preterm infants" Pediatrics 147 (6): e2021051485.
[3] This memorandum does not address whether products containing live microorganisms may also be regulated as a drug and/or biologic.

use in foods intended for pre-term infants. We are not aware of an applicable exception under section 201(s) of the FD&C Act for use of live microorganisms in foods for pre-term infants, other than the exception for dietary ingredients in dietary supplements [section 201(s)(6)]. Therefore, unless the substance is intended for use as a dietary ingredient in a dietary supplement,[4] the intended use of live microorganisms in foods intended for pre-term infants must be GRAS to be lawful. However, for the reasons described below, we are not aware of a basis to conclude as GRAS any use of any species of live microorganism in foods intended for pre-term infants. In fact, this use in food for pre-term infants may be harmful.

GRAS status requires publicly available evidence that the intended use is safe and a consensus among qualified experts that the intended use is safe (21 CFR 170.30). The information on the use of live microorganisms (a.k.a. "probiotics") by pre-term infants in the scientific literature raises serious safety concerns, some of which we will note here. Pre-term infants are a highly susceptible, heterogenous subpopulation of varying ages (<37 weeks of gestation) and weight, who are physiologically, developmentally, and metabolically immature compared to healthy term infants, resulting in their having a high risk for morbidity and mortality and requiring specialized care; thus, we have greater safety concerns for this population than we have for a healthy term infant population.[5] Because their gastrointestinal system is not fully matured, pre-term infants have more permeable intestinal linings, often referred to as "leaky guts," and motility problems, which can lead to opportunistic infections and sepsis when ingesting live microorganisms.[6] Further, it is reported by Katkowska et al., "The increased incidence of sepsis in neonates, compared to other pediatric cases or adult cases, suggests that immune deficiency may put this population at a high risk of probiotic sepsis."[7] The current and conflicting published literature does not support that the use of live microorganisms in pre-term infants is GRAS. For example, the American Academy of Pediatrics does not endorse the routine use of live microorganisms in pre-term infants, finding conflicting data on its safety and efficacy in this vulnerable population, particularly those with birth weight <1000 grams.[8]

We are also aware of recent adverse event reports associated with products containing live microorganisms:

- Fatality report of a pre-term infant ( ) associated with Infinant Health's[9] EVIVO with MCT oil, which contains *Bifidobacterium longum* subsp. *infantis* "EVC001." Genomic sequencing data demonstrate the bacterium that caused sepsis in this infant was a genetic match to the bacteria contained in this product.

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[4] Whether a particular live microorganism qualifies as a dietary ingredient is not the subject of this memorandum.
[5] Engle et al. (2007) "Late-preterm' infants: a population at risk" 120: 1390; Blencowe et al. (2013) "Born Too Soon: The global epidemiology of 15 million preterm births" Reproductive Health 10: S2; Pavlyshyn et al. (2023) "Developmental care advantages in preterm infant management" Journal of Neonatal Nursing 29: 117.
[6] Fleming et al. (2019) "Addressing safety concerns of probiotic use in preterm babies" Early Human Development 135: 72; Jiang et al. (2022) "Development of the digestive system in early infancy and nutritional management of digestive problems in breastfed and formula-fed infants" Food & Function 13: 1062; Indrio et al. (2022) "Development of the Gastrointestinal Tract in Newborns as a Challenge for an Appropriate Nutrition: A Narrative Review" Nutrients 14: 1405.
[7] Katkowska et al. (2021) "Probiotics: should all patients take them?" Microorganisms 9: 2620.
[8] Poindexter (2021) "Use of probiotics in preterm infants" Pediatrics 147 (6): e2021051485.
[9] Formerly Evolve BioSystems, Inc.

- Hyperglycemia and metabolic acidosis report of a pre-term infant ( ) associated with Abbott's Similac Probiotic Tri-blend, which contains *Streptococcus thermophilus* (TH-4®). CFSAN's bioinformatic analysis confirmed that *S. thermophilus* (TH-4®) in the Abbott product and the clinical isolate collected from the infant are identical.

In light of the safety concerns for pre-term infants and lack of GRAS status for this use, products containing live microorganisms in foods (excluding a dietary ingredient in a dietary supplement) intended for pre-term infants are adulterated within the meaning of section 402(a)(2)(C)(i) of the Act because their use is an unsafe food additive within the meaning of Sections 201(s) and 409 of the Act.