Memorandum

Date	September 28, 2023
From	(HFS-255) Through (HFS-255) (HFS-255)
Subject	Regulatory Status of Infinant Health *Bifidobacterium longum* subsp. *infantis* "EVC001" (EVIVO with MCT oil) when intended for consumption by pre-term infants
To	Administrative File, GPS 000220

This memorandum concerns a recent fatality report of a pre-term infant ( ) associated with Infinant Health's[1] EVIVO with MCT oil, which contains *B. longum* subsp. *infantis* "EVC001." Infinant Health markets EVIVO with MCT oil for health care settings and the product's "feeding instructions" are that it is for "enteral or oral use only." CFSAN's Office of Compliance (OC) asked the Office of Food Additive Safety (OFAS)'s Division of Food Ingredients (DFI) whether Infinant Health's product, when intended for consumption by pre-term infants, is adulterated within the meaning of section 402(a)(2)(C)(i) because this use of *B. longum* subsp. *infantis* "EVC001" is an unsafe food additive within the meaning of sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic (FD&C) Act.[2]

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 contains an unapproved/unsafe food additive is adulterated under the FD&C Act. We have not issued a regulation authorizing use of *B. longum* subsp. *infantis* "EVC001" as a food additive. We are not aware of an applicable exception under section 201(s) of the FD&C Act for use of *B. longum* subsp. *infantis* "EVC001" in conventional foods or infant formula. Therefore, the intended use of *B. longum* subsp. *infantis* "EVC001" in food, including infant formula, 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

[1] Formerly Evolve BioSystems, Inc.
[2] This memorandum does not address whether this product may also be regulated as a drug and/or biologic.

as GRAS any use of *B. longum* subsp. *infantis* "EVC001" in food, including infant formula, 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 living 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.[3] 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 living microorganisms.[4] The current and conflicting published literature does not support that the use of living microorganisms in pre-term infants is GRAS. For example, the American Academy of Pediatrics does not endorse the routine use of living microorganisms in pre-term infants, finding conflicting data on its safety and efficacy in this vulnerable population, particularly those with birth weight <1000 grams."[5] These safety concerns, among other regulatory concerns, were previously communicated during a meeting held between DFI and Infinant Health on July 7, 2023 (GPS 000220). In particular, we questioned if the clinical studies were robust enough to support safety, as the studies were short-term, poorly designed, and difficult to interpret without appropriate controls. We also noted that short-term clinical studies, in general, are only supportive evidence of safety for the use of living microorganisms and have not served as the primary basis for safety in any GRAS conclusions to date for the use of living microorganisms that have come through the GRAS Notification program.

In light of the safety concerns for pre-term infants and lack of GRAS status for this use, Infinant Health's EVIVO with MCT oil product is adulterated within the meaning of Section 402(a)(2)(C)(i) of the Act because their use of *B. longum* subsp. *infantis* "EVC001" in this product is an unsafe food additive within the meaning of Sections 201(s) and 409 of the Act.

Attachment(s): Memorandum of meeting dated 07/07/2023 (GPS 000220)

[redacted]

[3] 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.
[4] 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.
[5] *Pediatrics* (2021) 147 (6): e2021051485.