



Luc Sterkman, MD
Caelus Health
Rondweg 50
3474 KG Zegveld
NETHERLANDS

Re: GRAS Notice No. GRN 001065

Dear Dr. Sterkman:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001065. We received Caelus Health's notice on April 4, 2022, and filed it on July 27, 2022. Caelus Health submitted amendments to the notice on November 2, 2022, January 30, 2023, and April 5, 2023, including additional information regarding the identity, intended use, manufacturing method, specifications, dietary exposure, and safety of the ingredient.

The subject of the notice is *Anaerobutyricum soehngenii* strain CBS 145175 (*A. soehngenii* CBS 145175) for use as an ingredient in sports drinks and fluid replacement drinks; ready-to-eat breakfast cereals; cereal, granola, "energy," protein, and meal-replacement bars; ice cream; plain fermented milk; yogurt (including non-dairy yogurt); nut spreads; and chocolate at a maximum level of 1.0×10^{10} total fluorescent unit (TFU)/serving.¹ The notice informs us of Caelus Health's view that these uses of *A. soehngenii* CBS 145175 are GRAS through scientific procedures.

Caelus Health describes *A. soehngenii* CBS 145175 as a white to off-white powder. Caelus Health states that *A. soehngenii* CBS 145175 is a strictly anaerobic, Gram-positive, rod-shaped bacterium. Caelus Health discusses the results of the phenotypic and genotypic characterization of *A. soehngenii* CBS 145175 and states that the strain is non-pathogenic and non-toxigenic and is deposited in the Westerdijk Fungal Biodiversity Institute culture collection in Utrecht, Netherlands. Caelus Health discusses the results of the genomic and bioinformatic analyses performed on *A. soehngenii* CBS 145175 and states that no antibiotic resistance genes or genes encoding virulence factors or allergenic proteins were identified.

Caelus Health states that the parent strain, *A. soehngenii* strain DSM 17630 (*A. soehngenii* DSM 17630), was isolated from infant feces and is known to be resistant to the antibiotic tetracycline. *A. soehngenii* CBS 145175 was constructed by treating the

¹ Caelus Health states that *A. soehngenii* CBS 145175 is not intended for use in infant formula, infant foods, products under the jurisdiction of the United States Department of Agriculture or in foods for which standards of identity preclude its use.

parent strain with ethyl methanesulfonate resulting in a frameshift mutation in the gene conferring tetracycline resistance. The resulting strain, *A. soehngenii* CBS 145175, produces a truncated TetO protein and is therefore susceptible to tetracycline.

Caelus Health describes the manufacture of *A. soehngenii* CBS 145175 by fermentation of a pure culture under controlled conditions. After fermentation, cells are harvested by centrifugation or crossflow filtration and washed. Cryoprotectants² are added to the concentrated cell mixture that is then lyophilized, ground, and mixed with maltodextrin to obtain the final product. Caelus Health states that *A. soehngenii* CBS 145175 is manufactured under current good manufacturing practices using food-grade materials. Caelus Health states that no components of the fermentation media are allergens or are derived from allergenic sources.

Caelus Health provides specifications for *A. soehngenii* CBS 145175 that include total cell count ($\geq 5.0 \times 10^9$ TFU/g), viable cell count ($\geq 1.0 \times 10^8$ active fluorescent units/g), and limits for heavy metals, including lead (< 0.1 mg/kg), and limits for microorganisms, including aerobic mesophilic bacteria ($< 5.0 \times 10^3$ colony forming units (CFU)/g), yeasts and molds (< 100 CFU/g), *Salmonella* serovars (absent in 10 g), *Listeria monocytogenes* (absent in 10 g), *Bacillus cereus* (< 500 CFU/g), *Enterobacteriaceae* (< 100 CFU/g), *Staphylococcus aureus* (< 100 CFU/g), and sulfite reducing anaerobic bacteria (< 100 CFU/g). Caelus Health provides the results from the analyses of three non-consecutive batches to demonstrate that *A. soehngenii* CBS 145175 can be manufactured to meet the specifications.

Caelus Health determines that the highest number of food servings that may contain *A. soehngenii* CBS 145175 is 10 servings/d for the adult male population. Based on this assumption, Caelus Health estimates the maximum dietary exposure to *A. soehngenii* CBS 145175 from the intended uses to be 1.0×10^{11} TFU/day.

Caelus Health discusses the safety of *A. soehngenii* CBS 145175 and the parent strain, *A. soehngenii* DSM 17630. Caelus Health summarizes a published toxicological study using *A. soehngenii* CBS 145175, which included genetic toxicity studies and a 90-day subchronic oral toxicity study in rats. Caelus Health notes that no test-article related adverse events or genotoxicity were observed. Caelus Health discusses the results of published clinical studies in which adults were fed the parent strain, *A. soehngenii* DSM 17630, and states that the strain was well tolerated with no adverse events reported. Further, Caelus Health discusses unpublished *in silico* analysis on the potential for allergenicity and concludes that *A. soehngenii* CBS 145175 has a low allergenic potential. Caelus Health states that no information contradicting their GRAS conclusion was identified when a comprehensive literature search was performed.

Based on the totality of the data and information, Caelus Health concludes that *A. soehngenii* CBS 145175 is GRAS for its intended use.

² In an amendment dated January 30, 2023, Caelus Health states that sucrose, maltodextrin, and sodium chloride are the only cryoprotectants that will be used in the manufacturing process of *A. soehngenii* CBS 145175.

Standards of Identity

In the notice, Caelus Health states its intention to use *A. soehngenii* CBS 145175 in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing *A. soehngenii* CBS 145175 bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of Caelus Health's notice concluding that *A. soehngenii* CBS 145175 is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing *A. soehngenii* CBS 145175. Accordingly, our response should not be construed to be a statement that foods containing *A. soehngenii* CBS 145175, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Caelus Health provided, as well as other information available to FDA, we have no questions at this time regarding Caelus Health's conclusion that *A. soehngeni* CBS 145175 is GRAS under its intended conditions of use. This letter is not an affirmation that *A. soehngeni* CBS 145175 is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001065 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Susan J.
Carlson -S**

Digitally signed by Susan J.
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