



Elizabeth Lewis, Ph.D.
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UNITED KINGDOM

Re: GRAS Notice No. GRN 001129

Dear Dr. Lewis:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001129. We received the notice that you submitted on behalf of Superbrewed Food, Inc. (Superbrewed Food) on December 14, 2022, and filed it on June 22, 2023. Superbrewed Food submitted amendments to the notice on October 24, 2023, December 7, 2023, and February 14, 2024, clarifying information about the intended uses, manufacturing process, specifications, raw materials and processing aids, dietary exposure, amino acid scores, and allergenicity.

The subject of the notice is heat-killed *Clostridium tyrobutyricum* SD20/06 (HK-C. *tyrobutyricum* SD20/06) for use as a source of protein in the food categories as described in Table 1.¹ The notice informs us of Superbrewed Food's view that this use of HK-C. *tyrobutyricum* SD20/06 is GRAS through scientific procedures.

Table 1
Intended food uses and maximum use levels for HK-C. *tyrobutyricum* SD20/06

Food Category	Food Uses	Maximum Use Level (%)
Grain products and pastas	Cereal and granola bars, meal replacement bars, nutritional bars, energy bars (not specifically marketed as high protein)	20
	High protein bars	40
	Biscuits, chips, crackers Breads, rolls, bagels, muffins Dried pasta and noodles Ready-to-eat (RTE) breakfast cereals	10

¹ Superbrewed Food states that HK-C. *tyrobutyricum* SD20/06 is not intended for use in infant formula, any products under the jurisdiction of the United States Department of Agriculture, or in foods where standards of identity preclude its use.

Food Category	Food Uses	Maximum Use Level (%)
	RTE breakfast cereals (granola, muesli and high protein)	15
Beverages and beverage bases	Ready-to-drink (RTD) non-milk based nutritional beverages and weight control drinks	15
	RTD non-milk-based protein beverages Protein-enriched fruit and vegetable smoothies and juices	20
	Protein powders (non-milk based)	90 (powder before reconstitution)
Dairy products	Milk-based nutritional beverages and weight control drinks RTD milk-based protein beverages	10
	Protein powders (milk-based)	90 (powder before reconstitution)
	Chocolate milks, hot chocolate, latte coffees and related drinks	8.5
Dairy product analogs	Non-dairy cheeses, cream cheeses, spreads, and dips	20
	Non-dairy cream and sour cream (liquid and powder)	5 (liquid) 20 (powder)
	Non-dairy yogurts and drinkable yogurts	15
	Non-dairy ice-cream, refrigerated desserts, frozen desserts, and whipped toppings Imitation milks	10
	Non-milk coffee whiteners/creamers	10 (powder) 1 (liquid)
Prepared meals and soups	RTE meals	15
	Soups (creamed vegetable soups only)	10
Plant protein products including meat and poultry analogs	Meat substitutes (burgers, “chicken” nuggets, sausages, lunch meat)	40
Fats and oils	Salad dressings, spreads, sauces	5
	High protein sauces	15
Confectionary	Gummies, chewy candies, hard candies, marshmallows	20

Our use of the term, “heat-killed *Clostridium tyrobutyricum* SD20/06” or “HK-C. *tyrobutyricum* SD20/06” in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with

FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient 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 (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "heat-killed *Clostridium tyrobutyricum* SD20/06" or "HK-*C. tyrobutyricum* SD20/06."

Superbrewed Food describes HK-*C. tyrobutyricum* SD20/06 as an off-white powder containing $\geq 80\%$ protein. Superbrewed Food states that HK-*C. tyrobutyricum* SD20/06 is a non-pathogenic and non-toxigenic Gram-positive, rod-shaped, anaerobic bacterium. Superbrewed Food states that HK-*C. tyrobutyricum* SD20/06 is deposited in the CABI culture collection and that whole genome 16S rDNA gene sequence analyses were conducted to confirm the identity.

Superbrewed Food describes the manufacture of HK-*C. tyrobutyricum* SD20/06. Ground corn is liquified using alpha-amylase. The hydrolyzed starch fraction of the liquified corn is separated from protein, fiber, and oil and subjected to further hydrolysis using glucoamylase to obtain a glucose feedstock. This hydrolysis step can occur before or simultaneously with the fermentation step. Alternatively, the liquified corn starch can be hydrolyzed with amylase and glucoamylase before separation from protein, fiber, and oil to obtain the glucose feedstock. The glucose feedstock obtained by either method is fermented with *C. tyrobutyricum* SD20/06 under controlled conditions. After fermentation, the biomass is separated from the fermentation medium by microfiltration, concentrated, heat-treated, washed, microfiltered, and dried to yield a powder. Superbrewed Food states that the manufacture of HK-*C. tyrobutyricum* SD20/06 is conducted in accordance with current good manufacturing practices (cGMP). Superbrewed Food states that all raw materials and processing aids are used in accordance with applicable U.S. regulations or are GRAS for their intended uses, and none of the raw materials and processing aids are derived from major food allergens.

Superbrewed Food provides specifications for HK-*C. tyrobutyricum* SD20/06 that include crude protein ($\geq 80\%$), moisture ($\leq 10\%$), crude fat ($\leq 3\%$), ash ($\leq 6\%$), carbohydrates ($\leq 8\%$), ammonia nitrogen ($\leq 1\%$), nucleic acids ($\leq 3\%$), lead (≤ 0.1 mg/kg), and limits for microorganisms. Superbrewed Food provides the results from the analyses of three non-consecutive batches to demonstrate that HK-*C. tyrobutyricum* SD20/06 can be manufactured to meet these specifications. Superbrewed Food states that HK-*C. tyrobutyricum* SD20/06 is stable for at least 12 months at 25 °C and 60% relative humidity.

Using food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES), Superbrewed Food estimates the eaters-only dietary exposures to HK-*C. tyrobutyricum* SD20/06 from the intended uses to be 10.8 g/person (p)/d at the mean and 26.1 g/p/d at the 90th percentile for the U.S. population aged 2 years and older. Superbrewed Food states that HK-*C. tyrobutyricum* SD20/06 is intended for use as a replacement for other protein ingredients and therefore, dietary

exposure to total protein is not expected to change.

Superbrewed Food discusses the publicly available data and information to support the safe use of HK-*C. tyrobutyricum* SD20/06. Superbrewed Food notes that *C. tyrobutyricum* is found in milk and cheese and has been identified as part of the human gut microbiome. Superbrewed Food discusses the fate of ingested protein and notes that the absorption, distribution, metabolism, and excretion of protein from HK-*C. tyrobutyricum* SD20/06 is expected to be the same as other proteins in the diet. Additionally, Superbrewed Food summarizes published toxicological studies using HK-*C. tyrobutyricum* SD20/06, the subject of this notice, as the test article, including a 14-day oral dose range-finding study, a 90-day oral toxicity study in rats, and genotoxicity studies. Superbrewed Food states that there were no test-article-related effects in the toxicity studies, nor was HK-*C. tyrobutyricum* SD20/06 found to be mutagenic or genotoxic in a bacterial reverse mutation assay or an *in vitro* mammalian micronucleus assay. As further corroborative evidence of safety, in an amendment dated October 24, 2023, Superbrewed Food discusses an unpublished human tolerability study done in adult males who consumed a single dose of HK-*C. tyrobutyricum* SD20/06. Superbrewed Food states that HK-*C. tyrobutyricum* SD20/06 was well tolerated, and no adverse events were reported.

Superbrewed Food addresses the allergenic potential of HK-*C. tyrobutyricum* SD20/06 and notes that a search of the literature through November 2022 yielded no reports of allergenicity associated with *C. tyrobutyricum*. Additionally, Superbrewed Food discusses a published bioinformatics analysis of the *C. tyrobutyricum* sequence and concludes that oral consumption of HK-*C. tyrobutyricum* SD20/06 is unlikely to result in allergenicity concerns. Superbrewed Food also discusses dietary exposure to nucleic acids from HK-*C. tyrobutyricum* SD20/06 consumption. Superbrewed Food notes that total nucleic acid dietary exposure would be less than 2 g/p/d and therefore, does not pose a safety concern.

Based on the totality of the data and information, Superbrewed Food concludes that HK-*C. tyrobutyricum* SD20/06 is GRAS for its intended use.

Standards of Identity

In the notice, Superbrewed Food states its intention to use HK-*C. tyrobutyricum* SD20/06 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 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 *HK-C. tyrobutyricum* SD20/06 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 ONFL in the Center for Food Safety and Applied Nutrition. OFAS 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 Federal Food, Drug, and Cosmetic Act (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 Superbrewed Food's notice concluding that *HK-C. tyrobutyricum* SD20/06 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 *HK-C. tyrobutyricum* SD20/06. Accordingly, our response should not be construed to be a statement that foods containing *HK-C. tyrobutyricum* SD20/06, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Superbrewed Food provided, as well as other information available to FDA, we have no questions at this time regarding Superbrewed Food's conclusion that *HK-C. tyrobutyricum* SD20/06 is GRAS under its intended conditions of use. This letter is not an affirmation that *HK-C. tyrobutyricum* SD20/06 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 001129 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

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