



Catherine Adams Hutt, Ph.D., R.D., C.F.S.
RdR Solutions Consulting, LLC
4568 Elm Bottom Circle
Aubrey, TX 76227

Re: GRAS Notice No. GRN 000831

Dear Dr. Hutt:

This letter corrects our letter signed August 13, 2019, sent in response to GRN 000831. The purpose of this revised letter is to correct the amendment dates listed in the first paragraph of our August 13, 2019, letter from June 20, 2019, June 23, 2019, and August 8, 2019, to July 20, 2019, July 23, 2019, and August 7, 2019, respectively.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000831. We received the notice that you submitted on behalf of Deerland Probiotics and Enzymes (Deerland) on December 7, 2018, and filed it on February 28, 2019. Deerland submitted amendments to the notice on April 30, 2019, May 24, 2019, July 20, 2019, July 23, 2019, and August 7, 2019, that clarified language in Parts 1, 4, and 5 of the notice, the intended use, manufacturing, the literature discussion, and withdrew the intended use in alcoholic beverages.

The subject of the notice is *Bacillus subtilis* DE111 spore preparation for use as an ingredient in cow's-milk and soy-based non-exempt infant formula for term infants at a maximum level of 2×10^8 colony forming units (CFU)/100 mL and in baked goods and baking mixes; beverages and beverage bases; breakfast cereals; chewing gum; coffee and tea; condiments and relishes; confections and frostings; dairy product analogs; fats and oils; fruit juices; frozen dairy desserts and mixes; fruit and water ices; gelatins, puddings, and fillings; grain products and pastas; soft/hard candy and cough drops; herbs, seeds, spices, seasonings, blends, extracts, and flavorings; jams and jellies; milk and milk products; nuts and nut products; plant protein products; processed fruits; processed vegetables and vegetable juices; snack foods; soups and soup mixes;¹ sugar; and sweet sauces, toppings, and syrups at levels from 1×10^6 to 1×10^{10} CFU/serving. The notice informs us of Deerland's view that these uses of *B. subtilis* DE111 spore preparation are GRAS through scientific procedures.

Our use of the term, "*Bacillus subtilis* DE111 spore preparation" or "*B. subtilis* DE111 spore preparation" in this letter is not our recommendation of that term as an

¹Deerland states that *B. subtilis* DE111 spore preparation is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.

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 "*Bacillus subtilis* DE111 spore preparation" or "*B. subtilis* DE111 spore preparation."

Deerland states that *B. subtilis* DE111 spore preparation is a Gram-positive, spore-forming, rod shaped bacterium, which is deposited in the strain collection of the United States Department of Agriculture National Center for Agricultural Utilization Research. Deerland discusses the results of phenotypic and genotypic characterizations used to confirm the strain's identity.

Deerland describes the manufacture of *B. subtilis* DE111 spore preparation by fermentation of a pure culture under controlled conditions. After fermentation, the medium is pasteurized to inactivate vegetative cells, concentrated, and dried to produce a granular powder spore preparation. Deerland states that *B. subtilis* DE111 spore preparation is manufactured with food-grade or FDA-approved materials under current good manufacturing practices. Deerland states that no components of manufacturing are allergens or derived from allergenic sources.

Deerland provides specifications for *B. subtilis* DE111 spore preparation that include a minimum of 2×10^8 CFU and limits for other microorganisms, including yeast and molds (≤ 300 CFU/g), *Salmonella* serovars (absent in 25 g), and *Cronobacter sakazakii* (absent in 10 g). Deerland states that *B. subtilis* DE111 spore preparation will be manufactured to meet these specifications. Additionally, Deerland provides data to demonstrate that *B. subtilis* DE111 spore preparation is stable for up to two years in storage and viable in acidic conditions.

Deerland estimates the exposure to *B. subtilis* DE111 spore preparation from infant formula and conventional foods. Deerland states that the highest energy consumption of infant formula (as consumed) at the 90th percentile is 213.4 mL/kg bodyweight (bw)/day (d) and estimates the exposure to be 4.27×10^8 CFU/kg bw/d. For conventional foods, Deerland states that on average, an individual consumes 20 servings of food/d; the highest consumption is 26 servings/d. Deerland estimates the exposure to be 1.3×10^{11} CFU/d based on 50% of food servings/d containing *B. subtilis* DE111 spore preparation.

Deerland discusses the safety of *B. subtilis* DE111 spore preparation, including the results of published animal studies demonstrating that consumption of *B. subtilis* does not induce acute or subacute toxicity. Deerland discusses the results of clinical studies where *B. subtilis* was administered to healthy children or adults and reports that no relevant adverse reactions were observed. Deerland discusses published reports of opportunistic infections in immunocompromised individuals and states that these do

not present a safety concern for *B. subtilis* DE111 spore preparation.

Deerland discusses the history of use of the *B. subtilis* strain and published literature demonstrating that *B. subtilis* is found in soil and has been isolated from the healthy human gastrointestinal tract and human breast milk. Deerland states that *B. subtilis* is non-pathogenic and non-toxicogenic. Deerland discusses the results of unpublished studies demonstrating that *B. subtilis* DE111 spore preparation is susceptible to antibiotics and lacks antibiotic resistance genes. Additionally, Deerland states that *B. subtilis* DE111 spore preparation does not possess hemolytic activity. Deerland notes the safety assessment of other authoritative bodies as support for the safe use of *B. subtilis* DE111 spore preparation.

Deerland includes the statement of a panel of individuals (Deerland's GRAS panel). Based on its review, Deerland's GRAS panel concluded that *B. subtilis* DE111 spore preparation is safe under the conditions of its intended use.

Based on the totality of evidence, Deerland concludes that *B. subtilis* DE111 spore preparation is GRAS for its intended use.

Standards of Identity

In the notice, Deerland states its intention to use *B. subtilis* DE111 spore preparation in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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 & Cosmetic (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). The notice raises a potential issue under these labeling provisions. In the notice, Deerland cites studies that describe *B. subtilis* DE111 spore preparation as having certain health benefits. If products containing *B. subtilis* DE111 spore preparation 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 ONFL. 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.

Intended Use in Infant Formulas

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to Deerland's GRAS notice does not

alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. subtilis* DE111 spore preparation to make the submission required by section 412. Infant formulas are the purview of ONFL.

Section 301(II) of the FD&C Act

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of Deerland's notice concluding that *B. subtilis* DE111 spore preparation is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing *B. subtilis* DE111 spore preparation. Accordingly, our response should not be construed to be a statement that foods containing *B. subtilis* DE111 spore preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Deerland provided, as well as other information available to FDA, we have no questions at this time regarding Deerland's conclusion that *B. subtilis* DE111 spore preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *B. subtilis* DE111 spore preparation 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 000831 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson - Digitally signed by Susan J.
Carlson -S
Date: 2019.10.07 13:03:48 -04'00'

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Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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and Applied Nutrition