Mr. Melvin S. Drozen
Keller and Heckman LLP
1001 G Street, NW, Suite 500W
Washington, DC 20005

Re: GRAS Notice No. GRN 000863

Dear Mr. Drozen:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000863. We received the notice that you submitted on behalf of Perfect Day, Inc. on May 20, 2019 and filed it on June 28, 2019. Perfect Day submitted amendments to the notice on July 3, August 14, September 10, and December 30, 2019, and January 28, 2020. These amendments provide additional information about the identity, manufacturing specifications, and intended use.

The subject of the notice is β-lactoglobulin produced by *Trichoderma reesei* (β-lactoglobulin) for use as a source of protein in food at levels up to 35%. Perfect Day states that β-lactoglobulin is not intended for use in infant formula or in products subject to regulation by the United States Department of Agriculture. The notice informs us of Perfect Day's view that this use of β-lactoglobulin is GRAS through scientific procedures.

Our use of the term, "β-lactoglobulin," 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 "β-lactoglobulin."

Perfect Day describes β-lactoglobulin as a white to cream colored powder containing β-lactoglobulin (> 90% of total protein). The preparation is produced through fermentation of the *T. reesei* production strain QM6a-PD1, which was constructed from *T. reesei* QM6a.

Perfect Day describes the construction of the production strain through targeted integration of an expression cassette carrying a gene codon-optimized for expression in *T. reesei* that encodes β-lactoglobulin identical to β-lactoglobulin from domestic cow (*Bos taurus*). Perfect Day confirmed the DNA insertion by PCR and its stability by evidence of β-lactoglobulin expression over multiple generations. Perfect Day confirmed the amino acid sequence identity of β-lactoglobulin by mass spectrometry and molecular weight by SDS-PAGE. Perfect Day further confirms that the production strain does not contain any antibiotic resistance genes or mobile genetic elements.

Perfect Day describes the manufacturing process for β-lactoglobulin by submerged fermentation of a pure culture of the production strain under controlled conditions. β-lactoglobulin is secreted into the fermentation media. After fermentation, the culture is subjected to centrifugation to separate the biomass from the fermentation media that contains soluble β-lactoglobulin. The pH is then adjusted to concentrate the β-lactoglobulin. An optional intermediate filtration and polishing step may be used to decrease impurities. The β-lactoglobulin is then concentrated via ultrafiltration/diafiltration and spray-dried to yield the final product. Perfect Day states that all raw materials, processing aids, filtration aids, and pH adjusters are safe and suitable and meet predefined quality standards.

Perfect Day provides specifications for β-lactoglobulin produced by fermentation as follows: protein Dumas/Kjeldahl (≥ 85% (wt)); β-lactoglobulin as % of protein (≥ 90%); moisture (< 6% (wt)); ash (< 3% (wt)); fat (< 1.5% (wt)); total carbohydrates (< 2% (wt)) and limits for heavy metals and microorganisms. Perfect Day provided analyses from three nonconsecutive lots to demonstrate that β-lactoglobulin produced by fermentation can be manufactured to meet the specifications.

Perfect Day provides a list of the typical food uses and use levels for β-lactoglobulin. Perfect Day states that β-lactoglobulin will substitute for traditional whey protein and other protein products in the marketplace, and therefore, the exposure to protein will not increase from this use.

Perfect Day addresses the safety of β-lactoglobulin produced via fermentation of *T. reesei* using a weight of the evidence approach that includes assessment of the safety of *T. reesei* and of the β-lactoglobulin preparation.

Perfect Day states that the β-lactoglobulin production strain is the filamentous fungus *T. reesei*. Perfect Day conducted a literature review and found no reports that implicate *T. reesei* with human, animal, or plant disease or allergenicity among healthy adults. On this basis, Perfect Day concludes that *T. reesei* is considered non-toxigenic, non-pathogenic, and non-allergenic. Perfect Day supports its conclusion using published scientific literature, the long history of safe use of *T. reesei* in industrial scale food enzyme production, and the results of bioinformatic analysis of *T. reesei* proteins conducted by the Food Allergy Research and Resource Program.

Perfect Day compares the notified substance, β-lactoglobulin produced from fermentation by *T. reesei*, to the protein found in bovine milk and isolated milk

proteins, which have a long history of safe consumption by humans of all ages. Perfect Day concludes that protein characterization data show that the sequence of β-lactoglobulin produced by fermentation is identical to commercially available bovine-produced β-lactoglobulin. Referring to a statement in GRN 000504[1], Perfect Day states that milk and milk proteins are of little toxicological concern to humans or animals. Perfect Day conducted a literature search and did not find any reported adverse effects other than reports of allergy.

Perfect Day states that because β-lactoglobulin produced by fermentation is identical to the protein found in bovine milk, it will produce a milk protein allergy when consumed by individuals with milk allergies. Perfect Day states that with the exception of milk-allergic individuals, β-lactoglobulin is not known to produce adverse effects.

Based on the long history of safe use of *T. reesei* in food ingredient production and the safe use of milk and milk protein as food, in combination with labeling to inform consumers about the presence of the milk allergen in foods containing β-lactoglobulin, Perfect Day concludes that β-lactoglobulin is GRAS for its intended use.

Standards of Identity

In the notice, Perfect Day states its intention to use β-lactoglobulin 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, 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 β-lactoglobulin 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. 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.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The

[1] Milk protein concentrate and milk protein isolate was the subject of GRN 000504. We evaluated this notice and responded in a letter dated November 21, 2014, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

FD&C Act defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. β-lactoglobulin produced by fermentation requires labeling under the FD&C Act because it contains protein derived from milk.

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 Perfect Day's notice concluding that β-lactoglobulin 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 β-lactoglobulin. Accordingly, our response should not be construed to be a statement that foods containing β-lactoglobulin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Perfect Day provided, as well as other information available to FDA, we have no questions at this time regarding Perfect Day's conclusion that β-lactoglobulin is GRAS under its intended conditions of use. This letter is not an affirmation that β-lactoglobulin 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 000863 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.03.25 15:14:13 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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