James T. Heimbach, Ph.D.
JHeimbach LLC
P.O. Box 66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 000829

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000829. We received the notice that you submitted on behalf of Cura Global Health, Inc. (Cura) on November 28, 2018, and filed it on March 6, 2019. Cura submitted amendments on October 17 and October 29, 2019. These amendments provided additional information regarding the dietary exposure estimate and method of manufacture.

The subjects of the notice are powdered *Aspergillus oryzae* grown with one or more added minerals (powdered *A. oryzae* with minerals) for use in conventional foods at a level that provides 25% of the Daily Value (DV) for each mineral contained in the product, up to 250 mg powder per serving.[1] In describing the use of powdered *A. oryzae* with minerals, Cura explains that these are intended for use in food categories consistent with FDA's Fortification Policy (21 CFR 104.20(a)). Cura states that powdered *A. oryzae* with minerals are not intended for use in infant and baby foods or foods regulated by the U.S. Department of Agriculture. The notice informs us of Cura's view that the intended uses of powdered *A. oryzae* with minerals are GRAS through scientific procedures.

Our use of the term, "powdered *A. oryzae* with minerals", in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substances 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 "powdered *A. oryzae* with minerals."

[1] For adults and children ages four years and older, as established in FDA's 2016 Food Labeling Final Rule (81 FR 33742; May 27, 2016).

Cura states that powdered *A. oryzae* with minerals are composed of the dried biomass of *A. oryzae* (Koji strain) and include products differentiated by mineral content. According to information in the notice, the biomass is mainly composed of protein and fiber with varying concentrations of one or more minerals dependent on the identity and amount of the mineral(s) added to the fermentation media as well as the fermentation time and conditions. Products described in GRN 000829 are:

- *A. oryzae* with iron (ferrous or ferric)
- *A. oryzae* with zinc
- *A. oryzae* with calcium
- *A. oryzae* with selenium
- *A. oryzae* with chromium
- *A. oryzae* with zinc, selenium, chromium, manganese, copper, and molybdenum
- *A. oryzae* with iron, zinc, selenium, chromium, manganese, copper, and molybdenum

Cura provides information about the method of manufacture of powdered *A. oryzae* with minerals. Briefly, a germinated seed culture of *A. oryzae* (Koji strain) is grown in a fermenter with liquid medium composed of food-grade processing aids and fermentation components, which are not derived from major food allergens. The medium is enriched with food- or US Pharmacopeia-grade minerals, including one or more of the following: potassium dihydrogen phosphate, magnesium sulfate heptahydrate, calcium carbonate, calcium acetate monohydrate, ferrous sulfate heptahydrate, ferric pyrophosphate, manganese sulfate monohydrate, cupric sulfate pentahydrate, chromic chloride hexahydrate, sodium molybdate dihydrate, sodium selenite anhydrous, and zinc sulfate heptahydrate. During fermentation, the temperature and pH of the culture are controlled, cell-growth is monitored, and samples are taken for quality control. At the end of fermentation, the temperature of the fermentation tank is raised to at least 65°C for approximately 20 minutes to kill the *A. oryzae* cells. Samples are tested to ensure completion of the kill step. The culture is filtered to separate the liquid medium from the *A. oryzae* biomass, which is mechanically broken, dried, and ground to produce a powder with the desired particle size.

Cura provides appearance and mineral content specifications for both single-mineral and multi-mineral products, as well as limits for heavy metals and microorganisms. Cura provides data for three non-consecutive batches to show that powdered *A. oryzae* with minerals can be produced according to the described method of manufacture and does not contain mycotoxins. Additionally, Cura provides data from a six-month, accelerated stability study demonstrating product characteristics (appearance, moisture, total plate count, and microbial content) are stable over the course of the study.

Cura describes the intended uses of six single-mineral formulations and two multi-mineral products of powdered *A. oryzae* with minerals in conventional foods, including nonalcoholic, non-carbonated beverages; breakfast cereals and bars; rice and pastas; powdered milk and yogurts; condiments; processed fruits and fruit juices; processed

vegetables and vegetable juices; soups and soup mixes; and nutritional drinks. Cura uses food consumption data reported in "What We Eat in America," a component of the National Health and Nutrition Examination Survey (NHANES). The surveys employed were conducted in 2011-2012 and 2013-2014. From these data, Cura estimates the mean and 90th percentile 2-day average dietary exposures (eaters-only) for the powdered *A. oryzae* portion of the notified substances. These estimates employ the 250 mg maximum use level per serving, which Cura states is for the multi-mineral and calcium products. The dietary exposure estimates, for the U.S. population over the age of 2 years, are 0.39 g at the mean and 0.78 g at the 90th percentile.[2]

Cura also estimated dietary exposures for each mineral based on the use levels of the single-mineral and multi-mineral products under the conditions of their intended use (i.e., to provide 25% of the DV per serving). According to information in the notice, the maximum estimated dietary exposure to each of the minerals ranges from approximately 56% at the mean and 112% at the 99th-percentile of the DV.[3]

Cura states that *A. oryzae* is an aerobic, filamentous fungus that forms asexual spores and has an optimal growth temperature of 32-36°C. Cura describes the long and safe use of *A. oryzae* in human food and states that it is regarded as non-pathogenic and non-toxigenic. Cura also describes the long history of use of *A. oryzae* in food fermentation industries and concludes industrial applications of *A. oryzae* are well recognized as being safe. Cura discusses published information on various *in vitro* and *in vivo* studies on enzymes and foods produced using *A. oryzae* as a production organism. None of the studies reported treatment-related adverse effects.

Cura summarizes published data on subchronic rat study and human trials with $FeSO_4$ and powdered *A. oryzae* with iron to support its safety. None of the studies reported treatment-related adverse effects.

Cura compared its estimated mean and 99th-percentile daily exposures for the individual minerals to the Tolerable Upper Intake Levels (ULs) established by the Institute of Medicine. Cura incorporates the scientific rationale for the ULs and concludes that they are protective of health by reference to the IOM reports. Cura reports that the mean daily exposure levels for each of the minerals is below the established ULs, as are all the estimated 99th-percentile dietary exposure with the exception of iron (which exceeds the UL by 3.6%). Given that (1) the iron content in the product ranges from 3-6% and (2) Cura used maximum iron content of 6% in its calculation, Cura concludes that the actual EDI for iron will be lower than its UL.

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[2] The use levels of the other single mineral product are lower, in order to provide approximately 25% of the DV of the specific mineral. Corresponding dietary exposures to the *A. oryzae* portion would be lower than these estimates.

[3] FDA notes that the 99th percentile estimates in the table provided by the notifier in the amendment dated Oct 17, 2019, are simply double the mean estimates. This type of modeling of high-percentile exposures is discussed in FDA's 2006 Guidance for Industry: Estimating Dietary Intake of Substances in Food. We have used the terms "pseudo-90th percentile" or simply "high percentile" to describe these estimates. A 99th percentile exposure would more likely be 5-10 times the mean, as these distributions are typically described by a log-normal function, with means and standard deviations of approximately the same amounts.

Cura includes the statement of a panel of individuals (Cura's GRAS panel). Based on its review, Cura's GRAS panel concluded that powdered *A. oryzae* with minerals are safe under the conditions of their intended use.

Based on the available scientific information, Cura concludes that powdered *A. oryzae* with minerals are GRAS for their intended use in foods.

Standards of Identity

In the notice, Cura states its intention to use powdered *A. oryzae* with minerals 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 powdered *A. oryzae* with minerals 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.

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 Cura's notice concluding that powdered *A. oryzae* with minerals are GRAS under their intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing powdered *A. oryzae* with minerals. Accordingly, our response should not be construed to be a statement that foods containing powdered *A. oryzae* with minerals, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Cura provided, as well as other information available to FDA, we have no questions at this time regarding Cura's conclusion that powdered *A. oryzae* with minerals are GRAS under their intended conditions of use. This letter is not an affirmation that powdered *A. oryzae* with minerals are 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 000829 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.12.09 14:29:10 -05'00'

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