



KG Rao  
DolCas Biotech, LLC  
9 Lenel Road  
Landing, NJ 07850

Re: GRAS Notice No. GRN 000686

Dear Mr. Rao:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000686. We received DolCas Biotech, LLC.'s (DolCas') notice on January 5, 2017, and filed it on February 1, 2017. We received your amendments to the notice containing additional information regarding the identity, specifications and safety studies for the subject of the notice on April 20, 2017, May 16, 2017, and May 19, 2017.

The subject of the notice is curcuminoids purified from the rhizomes of turmeric (*Curcuma longa* L.; curcuminoids)<sup>1</sup> for use as an ingredient in nutrition bars, yogurt, and smoothies at levels from 40 to 60 mg/serving and in medical foods at a level of 500 mg/serving. The notice informs us of DolCas' view that these uses of curcuminoids are GRAS through scientific procedures.

DolCas describes the identity and composition of curcuminoids. DolCas describes curcuminoids as a yellow-colored crystalline powder containing curcuminoids and purified essential oils of turmeric. The curcuminoids are composed of curcumin, desmethoxycurcumin, and bis-desmethoxycurcumin. The essential oils are composed of sesquiterpenes (aromatic (ar)-turmerone,  $\alpha$ -turmerone, and  $\beta$ -turmerone).

DolCas describes the manufacturing process for curcuminoids. DolCas states that turmeric rhizomes are dried and ground into a powder. Ethyl acetate is added to the turmeric powder to extract the curcuminoids. The extract is filtered and the ethyl acetate is removed by evaporation. The extract is cooled and the resulting curcuminoid crystals and the remaining liquid are separated by filtration. The crystals are then powdered. The liquid, which consists of essential oils and resin, is steam distilled to isolate the essential oils of turmeric. This essential oil fraction is further steam distilled to yield a concentrated fraction of ar-turmerone ( $\geq 45\%$ ). The curcuminoid powder is then blended with 5-7% purified essential oils and dried to produce the final product. DolCas states that all processing agents and materials used in the production of

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<sup>1</sup> Curcuminoids was the subject of GRN 000460, which informed FDA of the view of Sabinsa Corporation that curcuminoids is GRAS, through scientific procedures for use as a flavor, flavor enhancer, or an ingredient in baked goods, soups, snack foods, imitation dairy products, and seasoning at levels up to 20 mg per serving. FDA responded in a letter dated August 22, 2013, stating that the agency had no questions at that time regarding Sabinsa's GRAS conclusion.

curcuminoids are high-grade pure chemicals used in accordance with current good manufacturing practices.

DolCas provides specifications for curcuminoids. Specifications include a minimum content of total curcuminoids complex (>95%) consisting of curcuminoids and essential oils. Specifications also include a minimum content of curcuminoids (>86%), curcumin (>65%), particle size range (20-30 mesh), limits for moisture ( $\leq 2\%$ ), residual ethyl acetate ( $\leq 50$  mg/kg), arsenic (<1 mg/kg), lead (<0.5 mg/kg), mercury (<1 mg/kg), and for microbial contaminants. DolCas provides the results of five non-consecutive batch analyses of curcuminoids to demonstrate compliance with these specifications.

DolCas provides estimates of the dietary exposure to curcuminoids. DolCas estimates the dietary exposure to curcuminoids based on: 1) USDA's Foods Commonly Eaten in United States, quantities consumed per eating occasion and in a day, 1995-96, 2) USDA's Continuing Survey of Food Intakes by Individuals 1994-96 database and Diet and Health Knowledge Survey 1994-96, and 3) nutrient bar nutritional information. Based on these data, DolCas estimates the mean daily dietary exposure to be 91.26 mg/person (p)/day (1.5 mg/kg body weight (bw)/day), and the 90<sup>th</sup> percentile daily dietary exposure to be 182.51 mg/p/day (3.0 mg/kg bw/day).

DolCas also intends to use curcuminoids in medical foods at a level of 500 mg/serving. DolCas states that use in medical foods consists of up to 2 servings/day, is not intended for long term use and will only be used as necessary as directed by a physician.

DolCas discusses the published data and information supporting the safety of curcuminoids and states that a literature search was conducted through September 2016. DolCas discusses pharmacokinetic studies in animals and humans and states that curcumin has low bioavailability. DolCas discusses published studies specifically conducted with curcuminoids in combination with turmerone to support its safe use. These studies include an acute toxicity study in rats and mice, a 90-day subchronic oral toxicity study in rats, and *in vitro* genotoxicity studies. The results of the subchronic toxicity study showed that no adverse effects were observed at 1000 mg/kg bw/day, the highest dose tested. DolCas states that curcuminoids are neither mutagenic nor genotoxic. DolCas discusses a published two-generation reproductive toxicity study, which was also reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2004, in which male and female rats consumed diets containing up to 1100 mg/kg bw/day of curcumin and studied for two successive generations. Based on the results of this study, JECFA determined an acceptable daily intake of 3 mg/kg bw/day for curcumin. DolCas discusses several published human clinical studies demonstrating that consuming curcuminoids up to 8 g/day was well tolerated and did not elicit adverse effects.

DolCas summarizes published efficacy studies in mice and *in vitro* studies using turmerone that reported no adverse effects to corroborate the safety of curcuminoids.

DolCas includes the statement of a panel of individuals (DolCas' GRAS panel). Based on its review, DolCas' GRAS panel concluded that curcuminoids are safe under the conditions of its intended use.

Based on the totality of data and information summarized above, DolCas concludes that curcuminoids are GRAS under the conditions of its intended use.

### **Standards of Identity**

In the notice, DolCas states its intention to use curcuminoids 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). The notice raises a potential issue under these labeling provisions. In the notice, DolCas cites studies that describe curcuminoids as having certain health benefits. If products containing curcuminoids bear any nutrient content or health claims on the label or in labeling, such claims are the 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 (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.

### **Potential Requirement for a Color Additive Petition**

There is no GRAS provision for color additives. In the notice, DolCas notes that curcuminoids has color. As such, the use of curcuminoids in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 000686 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Petition Review in OFAS.

## **Medical Foods**

DolCas informed us of its intent to use curcuminoids in medical foods. Section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)) defines a medical food as a “food formulated to be consumed or administered enterally under a physician’s supervision.” This provision also specifies that a medical food is “intended for the specific dietary management of a disease or condition with distinctive nutritional requirements, based on recognized scientific principles, established by a medical evaluation.” Medical foods, including how they are labeled, are the purview of ONFL. OFAS did not consult with ONFL about whether any particular food product containing curcuminoids as an ingredient would be a medical food. Questions about medical foods should be addressed to 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 DolCas’ notice concluding that curcuminoids are GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing curcuminoids. Accordingly, our response should not be construed to be a statement that foods containing curcuminoids, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

## **Conclusions**

Based on the information that DolCas provided, as well as other information available to FDA, we have no questions at this time regarding DolCas’ conclusion that curcuminoids is GRAS under its intended conditions of use. This letter is not an affirmation that curcuminoids 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 000686 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Michael A. Adams -S

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A. Adams -S  
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