CFSAN201158

4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. FDA-2009-F-0570]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Vitamin D_2 Bakers Yeast

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of vitamin D_2 bakers yeast as a source of vitamin D_2 and as a leavening agent in yeast-leavened baked products at levels not to exceed 400 International Units (IU) of vitamin D_2 per 100 grams (g) in the finished food. This action is in response to a petition filed by Lallemand, Inc. (Lallemand).

DATES: This rule is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit either electronic or written objections and requests for a hearing by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section VII of this document for information on filing objections.

ADDRESSES: You may submit either electronic or written objections and requests for a hearing, identified by Docket No. FDA-2009-F-0570, by any of the following methods:

Electronic Submissions

Submit electronic objections in the following way:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.

Written Submissions

Submit written objections in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2009-F-0570. All objections received will be posted without change to http://www.regulations.gov, including any personal information provided. For detailed instructions on submitting objections, see the "Objections" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or objections received, go to http://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Introduction

In a notice published in the Federal Register of December 17, 2009 (74 FR 66979), FDA announced that a food additive petition (FAP 9A4779) had been filed by Lallemand, Inc., c/o Dennis T. Gordon, 117 N. Welcome Slough Rd., Puget Island, Cathlamet, WA 98612. The petition proposed to amend the food additive regulations in part 172--Food Additives Permitted for Direct Addition to Food for Human Consumption (21 CFR part 172), to provide for the safe use of vitamin D_2 bakers yeast as a dual purpose nutrient supplement and leavening agent or dough relaxer in yeast-containing baked products at levels not to exceed 400 IU of vitamin D_2 per 100 g in the finished food. The specific foods identified by the petition in which the additive will be used are yeast-leavened baked goods and baking mixes and yeast-leavened baked snack foods. After the notice was published, Lallemand amended the petition to exclude the proposed use of the additive as a dough relaxer.

Vitamin D[1], including Vitamin D_2, is affirmed as generally recognized as safe (GRAS) for use in food as a nutrient supplement in § 184.1950(c)(1) (21 CFR 184.1950(c)(1)) in accordance with § 184.1(b)(2) (21 CFR 184.1(b)(2)), with the following specific limitations:

Category of Food	Maximum Levels in Food (as served)
Breakfast cereals	350 IU/100 g
Grain products and pasta	90 IU/100 g
Milk	42 IU/100 g
Milk products	89 IU/100 g

[1] Vitamin D comprises a group of fat-soluble seco-sterols and comes in many forms. The two major physiologically relevant forms are vitamin D_2 and vitamin D_3. Vitamin D without a subscript represents either vitamin D_2 or vitamin D_3.

Additionally, under §§ 184.1950(c)(2) and (c)(3), vitamin D is affirmed as GRAS for use in infant formulas and margarine, respectively. Under § 172.380, vitamin D_3 is approved for use as a nutrient supplement in calcium-fortified fruit juices and fruit juice drinks; meal replacement and other type bars, soy protein-based meal replacement beverages represented for special dietary use in reducing or maintaining body weight; and cheese and cheese products as defined therein. Under § 172.379, vitamin D_2 is approved for use as a nutrient supplement in soy beverages, soy beverage products, soy-based butter substitute spreads, and soy-based cheese substitutes and soy-based cheese substitute products.

Vitamin D_2, also known as ergocalciferol, is the chemical 9,10-seco(5Z,7E,22E)-5,7,10(19),22-ergostatetraen-3-ol. The additive that is the subject of this petition is vitamin D_2 bakers yeast that is produced by exposing bakers yeast (Saccharomyces cerevisiae) to ultraviolet (UV) light, resulting in increased conversion of endogenous ergosterol to ergocalciferol. The vitamin D_2 in the UV light-treated bakers yeast is the same substance affirmed as GRAS in § 184.1950 and approved for use as a nutrient supplement in § 172.379.

Vitamin D is essential for human health. The major function of vitamin D is the maintenance of blood serum concentrations of calcium and phosphorus by enhancing the absorption of these minerals in the small intestine. Vitamin D deficiency can lead to abnormalities in calcium and bone metabolism such as rickets in children or osteomalacia in adults. Excessive intake of vitamin D elevates blood plasma calcium levels by increased intestinal absorption and/or mobilization from the bone.

To ensure that vitamin D is not added to the U.S. food supply at levels that could raise safety concerns, FDA affirmed vitamin D as GRAS with specific limitations as listed in § 184.1950. Under § 184.1(b)(2), an ingredient affirmed as GRAS with specific limitations may

be used in food only within such limitations, including the category of food, functional use, and level of use. Any addition of vitamin D to food beyond those limitations set out in § 184.1950 requires either a food additive regulation or an amendment of § 184.1950.

To support the safety of the proposed uses of vitamin D_2 bakers yeast, Lallemand performed analyses for the presence of any potential toxic precursor sterol components in UV light-treated bakers yeast. In addition, Lallemand submitted dietary intake estimates of vitamin D from the proposed uses of vitamin D_2 bakers yeast, currently-regulated uses of vitamin D, and from naturally-occurring sources of vitamin D. They compared these intake estimates to the Tolerable Upper Intake Level (UL) for vitamin D established by the Institute of Medicine (IOM) of the National Academies. Lallemand also submitted a number of publications pertaining to human clinical studies on vitamin D. Based on this information, which is discussed in section II of this document, Lallemand concluded that the proposed uses of vitamin D_2 bakers yeast in yeast-leavened baked products are safe.

II. Evaluation of Safety

A. UV Light-Treated Bakers Yeast

To support the safety of UV light-treated bakers yeast, Lallemand performed analyses to demonstrate that UV light treatment of bakers yeast does not produce additional sterols of toxicological concern. Lallemand provided chromatograms of extracts of UV light-treated and non-UV light-treated bakers yeast, and identified the substances present in the yeast extracts. One of the substances identified, tachysterol, is a photoisomer resulting from UV light treatment of the vitamin D precursor, pre-vitamin D. Tachysterol is a biologically inactive pre-vitamin form of vitamin D. Lallemand concluded that the small amount of tachysterol present in vitamin D_2 bakers yeast was insignificant and did not pose a toxicological concern.

A second photoisomer, lumisterol, is also typically formed from UV light treatment of pre-vitamin D. Lallemand reported that they did not detect lumisterol in the UV light-treated samples. Because tachysterol is reported as the predominant photoisomer produced at the UV wavelength used to make vitamin D_2 bakers yeast, it is reasonable that lumisterol would not be present at a detectable amount.

Other substances identified from the chromatograms were pre-vitamin D_2 (nonactive form of vitamin D_2), vitamin D_2, and ergosterol (naturally present in yeast). No other substances related to UV light treatment of bakers yeast were observed.

B. Vitamin D

To establish with reasonable certainty that a food additive is not harmful under its intended conditions of use, FDA considers the projected human dietary intake of the additive, the additive's toxicological data, and other relevant information (such as published literature) available to the Agency. FDA compares an individual's estimated daily intake (EDI) of the additive from all food sources to an acceptable intake level established by toxicological data. The EDI is determined by projections based on the amount of the additive proposed for use in particular foods and on data regarding the amount consumed from all food sources of the additive. The Agency commonly uses the EDI for the 90th percentile consumer of a food additive as a measure of high chronic dietary intake.

1. Estimated Daily Intake for Vitamin D

Lallemand provided mean and 90^{th} percentile vitamin D intake estimates for consumers of yeast-leavened baked products from: (1) The proposed food uses of vitamin D_2 bakers yeast; (2) current food uses of vitamin D (including regulated uses, naturally-occurring sources of vitamin D, and dietary supplements); and (3) combined current and proposed food uses.

Lallemand provided intake estimates for the overall U.S. population (1 year of age and older) and nine population subgroups (including infants less than 12 months of age). The Agency has determined that the methodology used to calculate these estimates is appropriate.

Lallemand's estimate of intake of vitamin D from all food sources for the overall U.S. population (1 year of age and older), including consumers of the yeast-leavened baked products identified in the petition, was 1,670 IU per person per day (IU/p/d) for the 90th percentile consumer. For the population subgroup of infants less than 12 months of age, including consumers of the yeast-leavened baked products identified in the petition, the dietary intake of vitamin D from all food sources was estimated to be 969 IU/p/d for the 90th percentile consumer. FDA concurs with these intake estimates.

2. Acceptable Intake Level for Vitamin D

In 1997, the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board at the IOM conducted an extensive review of toxicology and metabolism studies on vitamin D published through 1996. The IOM published a detailed report that included a UL for vitamin D for infants, children, and adults. At that time, the IOM established a UL for vitamin D of 2,000 IU/per day (p/d) for children 1 to 18 years of age and adults. The UL for all infants was 1,000 IU/p/d.

More recently, the IOM conducted an extensive review of relevant published scientific literature on vitamin D to update current dietary reference intakes and ULs for vitamin D. Based on more recent information, the IOM revised the ULs for vitamin D and developed a report on their findings.[2] In their current assessment of vitamin D, the IOM determined a UL of 1,000

[2] Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board, Institute of Medicine, "Dietary Reference Intakes for Calcium and Vitamin D," National Academies Press, Washington, DC, 2011.

IU/p/d for infants 0 months to 6 months of age and a UL of 1,500 IU/p/d for infants 6 months to 12 months of age. For children 1 year to 3 years of age, the UL was determined to be 2,500 IU/p/d; for children 4 years to 8 years of age, the UL was determined to be 3,000 IU/p/d. For children 9 years to 18 years of age and adults, the UL was determined to be 4,000 IU/p/d.

The IOM considers the UL as the highest usual intake level of a nutrient that poses no risk of adverse effects when the nutrient is consumed over long periods of time. The UL is determined using a risk assessment model developed specifically for nutrients and considers intake from all sources: food, water, nutrient supplements, and pharmacological agents. The dose-response assessment, which concludes with an estimate of the UL, is built upon three toxicological concepts commonly used in assessing the risk of exposures to chemical substances: No-observed-adverse-effect level, lowest-observed-effect level, and an uncertainty factor.

C. Safety Assessment

FDA reviewed and evaluated the information submitted by Lallemand regarding the safety of UV light-treated bakers yeast. FDA concludes that the use of UV light-treated bakers yeast does not pose a safety concern, since the UV light treatment has been shown not to produce any new components of toxicological concern that could be introduced into the diet (see section II.A of this document).

In addition, FDA reviewed and evaluated the information submitted by Lallemand regarding the safety of the dietary intake of vitamin D_2 that would result from the proposed uses of vitamin D_2 bakers yeast. Lallemand submitted scientific articles published subsequent to the 1997 IOM report and issuance of the March 16, 2009, final rule (74 FR 11019) for the use of vitamin D_2 in soy-based food products. Lallemand concluded that these recent publications

continue to support vitamin D supplementation in humans. FDA concurs with Lallemand's conclusion.

FDA considered the ULs established by the IOM relative to the intake estimates provided by Lallemand as the primary basis for assessing the safety of petitioned uses of vitamin D. FDA also reviewed the scientific articles submitted by Lallemand. Finally, FDA reviewed studies on vitamin D that have published since the Agency's evaluation of four previous food additive petitions for fortifying a variety of foods with vitamin D. The most recent petition resulted in FDA's amendment of the food additive regulations in § 172.379 to allow for the safe use of vitamin D_2 as a nutrient supplement in soy-based food products (74 FR 11019, March 16, 2009). The three earlier food additive petitions also resulted in amendments of the food additive regulations to allow for the safe use of vitamin D_3 as a nutrient supplement in certain foods (70 FR 69435, November 16, 2005; 70 FR 37255, June 29, 2005; 70 FR 36021, June 22, 2005; and 68 FR 9000, February 27, 2003).

Depending on the age group, the IOM ULs for the U.S. population 1 year of age and older range from 2,500 IU/p/d to 4,000 IU/p/d. The estimated intake of vitamin D from all food sources, including the proposed uses, at the 90th percentile for the overall U.S. population (1 year of age and older) is estimated to be 1,670 IU/p/d, which is below the lowest IOM UL in the range of ULs for the overall U.S. population (1 year of age and older). For infants less than 12 months of age, the estimated intake of vitamin D from all food sources, including the proposed uses, at the 90th percentile is 969 IU/p/d, which is below both the IOM UL of 1,000 IU/p/d for infants 0 months to 6 months of age and the IOM UL of 1,500 IU/p/d for infants 6 months to 12 months of age. Because the 90th percentile EDI of vitamin D from all current and proposed food sources calculated for each population group is less than the corresponding IOM UL for that

population group, the Agency concludes that dietary intake of vitamin D_2 bakers yeast from its proposed uses as a source of vitamin D_2 and as a leavening agent in yeast-leavened baked products will not pose a safety concern.

III. Conclusion

Based on all data relevant to vitamin D_2 bakers yeast reviewed by the Agency, FDA concludes that there is a reasonable certainty that no harm will result from the use of vitamin D_2 bakers yeast as a source of vitamin D_2 and as a leavening agent in yeast-leavened baked products within the limits proposed by Lallemand. Thus, vitamin D_2 bakers yeast is safe for the proposed uses, and the Agency concludes that the food additive regulations should be amended as set forth in this document.

IV. Public Disclosure

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition will be made available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person (see FOR FURTHER INFORMATION CONTACT). As provided in § 171.1(h), the Agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

V. Environmental Impact

The Agency has previously considered the environmental effects of this rule as announced in the notice of filing for FAP 9A4779 (74 FR 66979). No new information or comments have been received that would affect the Agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

VI. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Objections

Any person who will be adversely affected by this regulation may file with the Division of Dockets Management (see ADDRESSES) either electronic or written objections. Each objection must be separately numbered, and each numbered objection must specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested must specifically so state. Failure to request a hearing for any particular objection constitutes a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested must include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection constitutes a waiver of the right to a hearing on the objection. It is only necessary to send one set of documents. Identify documents with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

FDA's review of this petition was limited to section 409 of the FD&C Act (21 U.S.C. 348). This final rule is not a statement regarding compliance with other sections of the FD&C Act. For example, the Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amended the FD&C Act to, among other things, add

section 301(ll) (21 U.S.C. 331(ll)). 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 (21 U.S.C. 355), a biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), or a drug or biological product for which substantial clinical investigations have been instituted and their existence has been made public, unless one of the exemptions in section 301(ll)(1) to (ll)(4) of the FD&C Act applies. In our review of this petition, FDA did not consider whether section 301(ll) of the FD&C Act or any of its exemptions apply to food containing this additive. Accordingly, this final rule should not be construed to be a statement that a food containing this additive, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll) of the FD&C Act. Furthermore, this language is included in all food additive final rules and therefore should not be construed to be a statement of the likelihood that section 301(ll) of the FD&C Act applies.

List of Subjects in 21 CFR Part 172

Food additives, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 172 is amended as follows:

PART 172--FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

2. Section 172.381 is added to subpart D to read as follows:

§ 172.381 Vitamin D_2 bakers yeast.

Vitamin D_2 bakers yeast may be used safely in foods as a source of vitamin D_2 and as a leavening agent in accordance with the following prescribed conditions:

(a) Vitamin D_2 bakers yeast is the substance produced by exposing bakers yeast (Saccharomyces cerevisiae) to ultraviolet light, resulting in the photochemical conversion of endogenous ergosterol in bakers yeast to vitamin D_2 (also known as ergocalciferol or (9,10-seco(5Z,7E,22E)-5,7,10(19),22-ergostatetraen-3-ol)).

(b) Vitamin D_2 bakers yeast may be used alone as an active dry yeast concentrate or in combination with conventional bakers yeast.

(c) The additive may be used in yeast-leavened baked goods and baking mixes and yeast-leavened baked snack foods at levels not to exceed 400 International Units of vitamin D_2 per 100 grams in the finished food.

(d) To assure safe use of the additive, the label or labeling of the food additive container shall bear, in addition to the other information required by the Federal Food, Drug, and Cosmetic Act, adequate directions for use to provide a final product that complies with the limitations prescribed in paragraph (c) of this section.

(e) Labels of manufactured food products containing the additive shall bear, in the ingredient statement, the name of the additive, "vitamin D_2 bakers yeast," in the proper order of decreasing predominance in the finished food.

Dated: August 20, 2012.

Kirk B. Arvidson,

Acting Director,

Office of Food Additive Safety,

Center for Food Safety and Applied Nutrition.

[FR Doc. 2012-21353 Filed 08/28/2012 at 8:45 am; Publication Date: 08/29/2012]