DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

MAY 10 2013

Minoru Tanaka
President
Eisai Food & Chemical Co., Ltd.
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2-3-10 Nihonbashi Chuo-ku, Tokyo
103-0027 JAPAN

Re: GRAS Notice No. GRN 000441

Dear Mr. Tanaka:

The Food and Drug Administration (FDA) is responding to the notice, dated July 30, 2012, that Eisai Food & Chemical Co., Ltd. (Eisai) submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on August 8, 2012, filed it on August 23, 2012, and designated it as GRAS Notice No. GRN 000441.

The subject of the notice is sodium ferrous citrate. The notice informs FDA of the view of Eisai that sodium ferrous citrate is GRAS, through scientific procedures, for use in various food categories as a source of dietary iron for food enrichment and fortification purposes consistent with iron supplementation guidelines.[1]

As part of its notice, Eisai includes the report of a panel of individuals (Eisai's GRAS panel) that evaluated the data and information that are the basis for Eisai's GRAS determination. Eisai considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Based on this review, Eisai's GRAS panel concluded that sodium ferrous citrate that meets its established food grade specifications is GRAS under the conditions of its intended use.

Eisai provides information on the identity, composition, and method of manufacture for sodium ferrous citrate. Eisai describes sodium ferrous citrate as an odorless, green-white crystalline powder that is soluble in acidic solvents, practically insoluble in water, and insoluble in basic solvents. The CAS registry number is 50717-86-7, the chemical formula is $Na_4FeC_{12}H_{10}O_{14}$, and the formula weight is 526.01. Eisai reports that the average iron and sodium contents are 10.4 and 17.6%, respectively. Sodium ferrous citrate is produced in accordance with current good manufacturing practices (cGMP) by the water-based reaction of sodium citrate and ferrous sulfate. Methanol is added to the reaction product to precipitate the salt, which is subsequently dried and sieved to yield the final product. Eisai states that all materials and processing aids employed in the manufacture of sodium ferrous citrate are used in accordance with applicable U.S. regulations or are permitted for use in food.

[1] Eisai does not intend to use sodium ferrous citrate in fresh produce, infant formulas, meat, poultry, or fish products, sugars, or snack foods such as candies and carbonated beverages.

Eisai's product specifications for sodium ferrous citrate include iron content (10 to 11%) as well as limits for sulfate (≤ 0.48%), lead (≤ 1 milligrams per kilogram (mg/kg)), arsenic (≤ 4 mg/kg), and residual methanol (≤ 50 mg/kg). Eisai also examined the long-term stability of sodium ferrous citrate when stored for up to three years under ambient conditions and concluded that sodium ferrous citrate remained within specifications.

Eisai intends to market sodium ferrous citrate as a source of dietary iron in foods. Sodium ferrous citrate will be substituted for other iron sources in existing categories of foods fortified with other iron salts at levels consistent with iron supplementation guidelines. As examples of such use, Eisai cites ferric ammonium citrate, ferric citrate, ferric phosphate, ferric pyrophosphate, ferric sulfate, ferrous ascorbate, ferrous carbonate, ferrous citrate, ferrous fumarate, ferrous gluconate, ferrous lactate, and ferrous sulfate. These substances are affirmed GRAS for use as sources of dietary iron with no limitation other than cGMP (21 CFR Part184). Eisai states that the use of sodium ferrous citrate is in accordance with the Fortification Policy described in 21 CFR 104.20, and will be added to food at levels that are not expected to result in an excessive intake of iron. Eisai states that use of sodium ferrous citrate at levels significantly higher than those described in GRN 000441 would result in unfavorable color, odor, and taste of the food and concludes that the use of sodium ferrous citrate is self-limiting.

Eisai discusses the estimated dietary exposure of sodium ferrous citrate and of iron from other sources. Eisai notes that various iron-containing compounds have been considered GRAS for use in food as a source of dietary iron and fortification purposes via notification (GRNs 000152, 000178, and 000271) or affirmation. The reference daily intake (RDI) of iron is 18 mg/person/day (as per 21 CFR 101.9). Eisai states that iron fortification salts are typically added as a percentage of the RDI to supplement iron intake from the normal diet. The Institutes of Medicine (IOM) calculated recommended daily allowances and tolerable upper intake limits (ULs) for iron for different U.S. population groups. The adult UL is 45 mg/day; children up to the age of 13 were assigned a UL of 40 mg/day. IOM also estimated the mean and 90th percentile exposure of iron from all foods and supplements for all age groups to be 18.3 and 30.1 mg/person/day.

Eisai states that sodium ferrous citrate is intended for use as a replacement for other iron fortification salts at similar or lower levels in food, and concludes that the consumption of sodium ferrous citrate is not expected to significantly affect current dietary iron intakes. Therefore, the exposure of iron from sodium ferrous citrate is assumed to be similar to those estimated by IOM for all foods and supplements. Eisai notes that this is conservative as it assumes that sodium ferrous citrate would: 1) replace all iron currently available, including both naturally occurring, as well as supplemental; 2) be used in all food categories in which iron is present; and 3) be used at similar levels as other iron fortification salts.

Eisai discusses the potential dietary exposure of sodium from the use of sodium ferrous citrate and its comparison to total dietary sodium. Dietary exposures were calculated based on the sodium content of sodium ferrous citrate (17.6%) and the estimated mean and 90th percentile estimated dietary exposure for iron from all foods and supplements discussed above. Based on those assumptions and use levels, the estimated dietary exposure for sodium from use of sodium ferrous citrate was approximately 1% (31 mg/person/day at the mean) of total sodium intake.[2] Eisai therefore concludes that the use of sodium ferrous citrate is not expected to significantly increase dietary sodium levels.

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[2] Eisai cites the 2004 IOM estimate of sodium intake from the report "Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate," which was 3418 mg/day for the general population. FDA notes that more recent estimates are similar, and do not change Eisai's conclusion about the significance of sodium ferrous citrate as a source of sodium in the context of overall sodium intake.

Eisai discusses published safety data on sodium ferrous citrate and its components, including acute, subchronic, developmental and reproductive toxicity studies. Eisai also discusses human clinical studies related to the physiological effects of sodium ferrous citrate. Eisai reports that no adverse effects were observed at or below the UL established by IOM. Gastrointestinal disturbances were not observed in humans until dietary exposure exceeded four times the adult UL. Eisai concluded that the studies support the safety of the intended use of sodium ferrous citrate, which is not expected to result in intakes that exceed the UL of 40 mg/day for children and 45 mg/day for adults or cause appreciable increases in intake relative to IOM estimates of iron intake from all foods and supplements (about 18 mg/day at the mean and about 30 mg/day at the 90th percentile of exposure).

Potential Labeling Issues

In describing data and information on clinical studies that Eisai relies on to conclude that sodium ferrous citrate is GRAS under the conditions of its intended use, Eisai raises a potential issue under the labeling provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular. Section 403(r) of the FD&C Act lays out the statutory framework for the use of labeling claims that characterize the level of a nutrient in a food or that characterize the relationship of a nutrient to a disease or health-related condition. If products that contain sodium ferrous citrate bear any claims on the label or in labeling, such claims are the purview of the Office of Nutrition, Labeling, and Dietary Supplements (ONLDS) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (OFAS) neither consulted with ONLDS on this labeling issue nor evaluated the information in your notice to determine whether it would support any claims made about sodium ferrous citrate on the label or in labeling.

Potential Requirement for a Color Additive Petition

In its notice, Eisai describes sodium ferrous citrate as a replacement for other iron fortification salts, including ferrous lactate and ferrous gluconate. Ferrous lactate is affirmed for use both as a nutrient supplement and as a color fixative in ripe olives. Both ferrous lactate and ferrous gluconate are approved as color additives for use in ripe olives. Given the existing uses of other ferrous salts, use of sodium ferrous citrate in food products could constitute the use of a color additive 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), the term color additive means a material that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source, and that is capable (alone or through reaction with another substance) of imparting color when added or applied to a food; except that such term does not include any material which the Secretary,[3] by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. Under 21 CFR 70.3(g), a material that otherwise meets the definition of color additive can be exempt from that definition on the basis that it is used or intended to be used solely for a purpose or purposes other than coloring, as long as the material is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. Given the construct of section 201(t)(1) of the FD&C Act and 21 CFR 70.3(f) and (g), the use of a substance that is capable of imparting color may constitute use as a color additive in addition to use as a food additive or GRAS substance. For example, β-carotene is both approved for use as a color additive (21 CFR 73.95) and affirmed as GRAS for use as a nutrient supplement (21 CFR 184.1245); in some food products, β-carotene is used for both purposes. Importantly, if the use of sodium ferrous citrate constitutes use as a color additive within the meaning of section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR 70.3(f) and (g), section 721(a) of the FD&C Act requires premarket review and approval of that use by FDA. Under

[3] The Secretary of the Department of Health and Human Services.

section 402(c) of the FD&C Act, a food product that contains an unapproved color additive would be deemed adulterated.[4]

In its review of Eisai's notice that the sodium ferrous citrate is GRAS for the intended use as a source of dietary iron, FDA did not consider whether section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70 apply to the use of sodium ferrous citrate in foods. Accordingly, this response should not be construed to be a statement that the use of sodium ferrous citrate in foods is lawful under section 721(a). If, after receipt of this letter, Eisai has any further questions about this issue, we recommend that Eisai contact the Division of Petition Review in OFAS.

Section 301(ll) of the FD&C Act

The Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amends the FD&C Act to, among other things, add section 301(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, 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 its review of Eisai's notice that sodium ferrous citrate is GRAS for the intended use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing sodium ferrous citrate. Accordingly, this response should not be construed to be a statement that foods that contain sodium ferrous citrate, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by Eisai, as well as other information available to FDA, the agency has no questions at this time regarding Eisai's conclusion that sodium ferrous citrate is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of sodium ferrous citrate. As always, it is the continuing responsibility of Eisai to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

[4] We note that section 721(b)(4) of the FD&C Act provides that a color additive shall be deemed to be safe and suitable for the purpose of listing under section 721(b) of the FD&C Act while there is in effect a published finding of the Secretary declaring that the substance is exempt from the definition of "food additive" because of its being generally recognized by qualified experts as safe for its intended use as provided in section 201(s) of the FD&C Act. Importantly, FDA's response to GRN 000441 does not constitute a "finding of the Secretary" within the meaning of section 721(b)(4) of the FD&C Act.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000441, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying at www.fda.gov/grasnoticeinventory.

Sincerely,

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