



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. FDA-2017-C-6238]

Listing of Color Additives Exempt from Certification; Synthetic Iron Oxide

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending the color additive regulations to provide for the expanded safe use of synthetic iron oxides as color additives to include use in dietary supplement tablets and capsules. This action is in response to a color additive petition (CAP) filed by Colorcon, Inc.

DATES: This rule is effective December 4, 2018. See section X for further information on the filing of objections. Submit either electronic or written objections and requests for a hearing on the final rule by December 3, 2018.

ADDRESSES: You may submit objections and requests for a hearing as follows. Please note that late, untimely filed objections will not be considered. Electronic objections must be submitted on or before December 3, 2018. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of December 3, 2018. Objections received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic objections in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Objections submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your objection will be made public, you are solely responsible for ensuring that your objection does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your objection, that information will be posted on <https://www.regulations.gov>.
- If you want to submit an objection with confidential information that you do not wish to be made available to the public, submit the objection as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper objections submitted to the Dockets Management Staff, FDA will post your objection, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2017-C-6238 for “Listing of Color Additives Exempt from Certification; Synthetic Iron Oxide.” Received objections, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or with the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit an objection with confidential information that you do not wish to be made publicly available, submit your objections only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://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 Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Molly A. Harry, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740-3835, 240-402-1075.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a document published in the *Federal Register* on November 9, 2017 (82 FR 52037), we announced that we filed a color additive petition (CAP 7C0308) submitted by Colorcon, Inc., 275 Ruth Rd., Harleysville, PA 19438. The petition proposed to amend the color additive regulations in § 73.200 *Synthetic iron oxide* (21 CFR 73.200) by expanding the permitted uses of synthetic iron oxides as a color additive to include use in dietary supplement tablets and capsules, including coatings and printing inks. The petitioner requested that the proposed uses be permitted at a maximum use level of 5 milligrams (mg), calculated as elemental iron, per day for labeled dosages.

II. Background

Synthetic iron oxides and their hydrated forms are currently approved as color additives for use in human foods and drugs: (1) in sausage casings intended for human consumption in an amount not to exceed 0.10 percent by weight of the finished food (§ 73.200); (2) in soft and hard candy, mints, and chewing gum at levels consistent with good manufacturing practice (GMP),

except that they may not be used to color foods for which standards of identity have been issued under section 401 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 431) (FD&C Act), unless the use of the added color is authorized by such standards (§ 73.200); and (3) in ingested or topically applied drugs with a limit for ingested drugs of 5 mg, calculated as elemental iron, per day for labeled or prescribed dosages (21 CFR 73.1200). Synthetic iron oxides also are approved for use as color additives in cosmetics generally, including cosmetics applied to the area of the eye, in amounts consistent with GMP (21 CFR 73.2250).

Synthetic iron oxides and their hydrated forms include red iron oxide (synthetic hematite), yellow iron oxide (synthetic goethite), black iron oxide (synthetic magnetite), and brown iron oxide, which is a blend of various iron oxides. For the subject petition, synthetic iron oxides are intended for coloring dietary supplement tablets and capsules, including coatings for tablets and capsules and printing inks applied to dietary supplement tablets and capsules, such that the total amount of elemental iron in the dietary supplements does not exceed 5 mg per day for labeled dosages.

III. Safety Evaluation

Under section 721(b)(4) of the FD&C Act (21 U.S.C. 379e(b)(4)), a color additive cannot be listed for a particular use unless the data and information available to FDA establish that the color additive is safe for that use. FDA's color additive regulations in 21 CFR 70.3(i) define "safe" to mean that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive.

To establish with reasonable certainty that a color additive intended for use in foods is not harmful under its intended conditions of use, we consider the projected human dietary exposure to the color additive, the additive's toxicological data, and other relevant information

(such as published literature) available to us. We compare an individual's estimated exposure, or estimated daily intake (EDI), of the color additive from all sources to an acceptable daily intake level established by toxicological data. The EDI is determined by projections based on the amount of the color additive proposed for use in particular foods and on data regarding the amount consumed from all sources of the color additive. We commonly use the EDI for the 90th percentile consumer of a color additive as a measure of high chronic exposure.

IV. Safety of Petitioned Use of Color Additive

A. Estimated Dietary Exposure

To support the safety of the proposed use of synthetic iron oxides, Colorcon proposed a maximum use level of the color additive in dietary supplements such that the total amount of elemental iron consumed shall not exceed 5 mg per day for labeled dosages. Using 2-day food consumption data from the 2009-2010 National Health and Nutrition Examination Survey (NHANES) food consumption database, Colorcon estimated exposure to elemental iron from the proposed use in dietary supplements. From the NHANES data, Colorcon determined that 2 dietary supplements are consumed in a 24-hour period at the mean, and 4 at the 90th percentile. We note that these values could represent 2 or 4 different dietary supplements, respectively, with each supplement containing up to 5 mg elemental iron. Considering this, FDA has estimated exposure to elemental iron resulting from the petitioned use of synthetic iron oxides in dietary supplements as described below.

Using more recent NHANES data (2011-2014), FDA determined that the U.S. population aged 2 years and older consumes 2 dietary supplements per day at the mean and 5 supplements per day at the 90th percentile (Ref. 1). In estimating exposure, we presumed that: (1) each dietary supplement could contain up to 5 mg elemental iron for labeled dosages from the use of

synthetic iron oxides, resulting in an exposure to elemental iron of 10 milligrams per person per day (mg/p/d) at the mean and 25 mg/p/d at the 90th percentile; (2) all dietary supplements would contain added synthetic iron oxides; and (3) the added synthetic iron oxides would contain a maximum amount (72 percent) of elemental iron; therefore, the use level of 5 mg elemental iron per labeled dosage of dietary supplement would result in a use level of 6.9 mg synthetic iron oxides per labeled dosage of dietary supplement (Ref. 1).

We estimated an upper-bound exposure to synthetic iron oxides from its use as a color additive in dietary supplement tablets and capsules and in coatings applied to dietary supplement tablets and capsules, but excluding its use in printing inks applied on tablets and capsules, to be 13.8 mg/p/d at the mean and 34.5 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older (Ref. 1). The exposure to elemental iron from the petitioned use of synthetic iron oxides is estimated to be 10 mg/p/d at the mean and 25 mg/p/d at the 90th percentile. Regarding exposure to elemental iron resulting from the proposed use of synthetic iron oxides in printing inks applied on tablets and capsules, we estimated that the amount of elemental iron from the use of synthetic iron oxides in inks for use on tablets and capsules is no more than 5.4 micrograms (μg) per tablet or capsule, which corresponds to 10.8 μg elemental iron/p/d at the mean (2 tablets or capsules) and 27 μg elemental iron/p/d at the 90th percentile level (5 tablets or capsules) (Ref. 1). This exposure is negligible compared to that for use of elemental iron as a color additive in tablets and capsules and in coatings applied to dietary supplements.

In the final rule approving the use of synthetic iron oxides for use in candy, mints, and chewing gum (80 FR 14839, March 20, 2015), FDA discussed that elemental iron from synthetic iron oxides is not readily bioavailable and is poorly absorbed by the human gastrointestinal tract (80 FR 14839 at 14840). Approximately 18 percent of iron from conventional foods and dietary

supplements is bioavailable and about 1 percent of iron from synthetic iron oxides is bioavailable (Ref. 1). Taking into account the bioavailability of iron from synthetic iron oxides, the exposure to elemental iron from the petitioned use of synthetic iron oxides for the U.S. population aged 2 years and older is estimated to be 0.10 mg/p/d at the mean and 0.25 mg/p/d at the 90th percentile (Ref 1).

We previously estimated the cumulative exposure to bioavailable elemental iron for the U.S. population to be 3.48 mg/p/d at the mean (Ref. 1). Therefore, considering the exposure of 0.10 mg/p/d for elemental iron from the proposed use of synthetic iron oxides, the updated cumulative exposure to bioavailable iron from the current and proposed sources for the U.S. population aged 2 years and older is estimated to be 3.6 mg/p/d at the mean and 7.2 mg/p/d at the pseudo-90th percentile (Ref. 1).

B. Acceptable Intake Level for Iron

In 2001, the Institute of Medicine (IOM) published a report on dietary reference intakes for vitamins and minerals (Ref. 2). In the report, IOM determined dietary reference intakes and upper limits (ULs) for iron of 40 mg/d for children (2-13 years of age) and 45 mg/d for adolescents and adults (14 years and older) (Ref. 2). The IOM considers the UL as the highest daily intake level of a nutrient that poses no risk of adverse effects with chronic consumption of the nutrient (Ref 2). The UL is determined using a risk assessment model developed specifically for nutrients and may consider intake from such sources as food, water, nutrient supplements, and pharmacological agents (Ref 2). 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 (Ref. 2).

We considered the UL established by IOM for iron (45 mg/d) relative to the cumulative exposure for bioavailable elemental iron of 7.2 mg/p/d (at the 90th percentile for U.S. population 2 years and older) as the primary basis for assessing the safety of exposure to elemental iron from the proposed use of synthetic iron oxides (Ref. 3). Additionally, we reviewed scientific articles and other relevant studies available to FDA on the safety of iron (Ref. 3). Because the 90th percentile exposure estimate to bioavailable elemental iron from all dietary sources, including the proposed use of synthetic iron oxides to color dietary supplement tablets and capsules, is significantly below the UL determined by IOM, we conclude that there is a reasonable certainty of no harm from the proposed use of synthetic iron oxide as a color additive in dietary supplement tablets and capsules (Ref. 3).

V. Conclusion

FDA reviewed the data and information in the petition and other available relevant material and determined the petitioned use of synthetic iron oxides in dietary supplement tablets and capsules is safe. We further conclude that the color additive will achieve its intended technical effect and is suitable for the petitioned use. Consequently, we are amending the color additive regulations in 21 CFR part 73 as set forth in this document. In addition, based upon the factors listed in 21 CFR 71.20(b), we continue to conclude that certification of synthetic iron oxides is not necessary for the protection of public health.

VI. Public Disclosure

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see FOR FURTHER INFORMATION CONTACT). As

provided in § 71.15, we will delete from the documents any materials that are not available for public disclosure.

VII. Analysis of Environmental Impact

We previously considered the environmental effects of this rule, as stated in the November 9, 2017, *Federal Register* notification of petition for CAP 7C0308 (82 FR 52037). We stated that we had determined, under 21 CFR 25.32(k), that this action is of a type that does not individually or cumulatively have a significant effect on the human environment such that neither an environmental assessment nor an environmental impact statement is required. We have not received any new information or comments that would affect our previous determination.

VIII. 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.

IX. Section 301(ll) of the Federal Food, Drug, and Cosmetic Act

Our review of this petition was limited to section 721 of the FD&C Act. This final rule is not a statement regarding compliance with other sections of the FD&C Act. For example, 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 (4) of the FD&C Act applies. In our review of this petition, we did not consider whether section 301(ll) of the FD&C Act or any of its exemptions apply to food

containing this color additive. Accordingly, this final rule should not be construed to be a statement that a food containing this color 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 color additive final rules that pertain to food and therefore should not be construed to be a statement of the likelihood that section 301(ll) of the FD&C Act applies.

X. Objections

This rule is effective as shown in the “DATES” section, except as to any provisions that may be stayed by the filing of proper objections. If you will be adversely affected by one or more provisions of this regulation, you may file with the Dockets Management Staff (see ADDRESSES) either electronic or written objections. You must separately number each objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

Any objections received in response to the regulation may be seen in the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <https://www.regulations.gov>. We will publish notice of the objections that we have received or lack thereof in the *Federal Register*.

XI. References

The following references marked with an asterisk (*) are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. The reference without an asterisk is not on public display at <https://www.regulations.gov> because it has copyright restriction but is available at the website address. The reference without an asterisk is available for viewing only at the Dockets Management Staff. FDA has verified the website address, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

*1. Memorandum from D. Doell, Chemistry Review Team, Division of Petition Review, Office of Food Additive Safety (OFAS), Center for Food Safety and Applied Nutrition (CFSAN), FDA to M. Harry, Division of Petition Review, OFAS, CFSAN, FDA, September 17, 2018.

2. Institute of Medicine, “Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.” Washington, DC: National Academies Press (U.S.); 2001.

https://www.ncbi.nlm.nih.gov/books/NBK222310/pdf/Bookshelf_NBK222310.pdf.

*3. Memorandum from T. Thurmond, Toxicology Team, Division of Petition Review, OFAS, CFSAN, FDA to M. Harry, Division of Petition Review, OFAS, CFSAN, FDA, September 17, 2018.

List of Subjects in 21 CFR Part 73

Color additives, Cosmetics, Drugs, Foods, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 73 is amended as follows:

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

1. The authority citation for part 73 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

2. Section 73.200 is amended by revising paragraph (c)(1) to read as follows:

§ 73.200 Synthetic iron oxide.

* * * * *

(c) * * *

(1) Synthetic iron oxide may be safely used for human food use subject to the following restrictions:

(i) In sausage casings intended for human consumption in an amount not exceeding 0.10 percent by weight of the finished food.

(ii) In soft and hard candy, mints, and chewing gum at levels consistent with good manufacturing practice, except that it may not be used to color foods for which standards of identity have been issued under section 401 of the Federal Food, Drug, and Cosmetic Act, unless the use of the added color is authorized by such standards.

(iii) In dietary supplement tablets and capsules, including coatings and printing inks, such that the total amount of elemental iron per day for labeled dosages does not exceed 5 milligrams.

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Dated: October 26, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-23863 Filed: 10/31/2018 8:45 am; Publication Date: 11/1/2018]