



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. FDA-2018-C-4464]

Listing of Color Additives Exempt From Certification; Soy Leghemoglobin

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 safe use of soy leghemoglobin as a color additive in ground beef analogue products. We are taking this action in response to a color additive petition (CAP) submitted by Impossible Foods, Inc. (Impossible Foods or petitioner).

DATES: This rule is effective September 4, 2019. 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 [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

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 [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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-2018-C-4464 for “Listing of Color Additives Exempt From Certification; Soy Leghemoglobin.” 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.” We 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: Ellen Anderson, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740-3835, 240-402-1309.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a notice published in the *Federal Register* of December 13, 2018 (83 FR 64045), we announced that we filed a color additive petition (CAP 9C0314) submitted by Impossible Foods, Inc., c/o Exponent, Inc., 1150 Connecticut Avenue NW, Suite 1100, Washington, DC 20036. The petition proposed to amend the color additive regulations in part 73 (21 CFR part 73), “Listing of Color Additives Exempt from Certification” to provide for the safe use of soy leghemoglobin as a color additive in ground beef analogue products such that the amount of soy leghemoglobin protein does not exceed 0.8 percent by weight of the uncooked ground beef analogue product. For the purposes of this final rule, the term “ground beef analogue products” refers to plant-based or other non-animal derived ground beef-like food products. The petition describes soy leghemoglobin protein as the principal reddish brown coloring component of a stabilized mixture, referred to as soy leghemoglobin preparation. We are establishing soy

leghemoglobin as the common or usual name for this color additive and note that the terms “soy leghemoglobin” and “soy leghemoglobin preparation” are used interchangeably when referring to the name of the color additive in this final rule and in our review memoranda (Refs. 1 and 2).

II. Background

The color additive that is the subject of this petition is the stabilized product of controlled fermentation of a non-pathogenic and non-toxicogenic strain of the yeast, *Pichia pastoris* (*P. pastoris*), genetically engineered to express soy leghemoglobin protein, the principal coloring component. Soy leghemoglobin gets its name from its source, the soybean root; it is a heme protein present in the nitrogen-fixing root nodules of leguminous plants. The color additive is manufactured by construction of the *P. pastoris* production strain, expression of soy leghemoglobin protein via fermentation, followed by concentration and stabilization of the expressed protein. Based on information in the petition, soy leghemoglobin preparation contains not more than 9 percent soy leghemoglobin protein, minor quantities of *P. pastoris* yeast proteins, and optional stabilizers sodium chloride and sodium ascorbate. The color additive is stored either as a frozen liquid or in a spray dried form. FDA concurs with the petitioner that the genetic modifications made to generate the non-toxicogenic and non-pathogenic production strain are well-characterized and the production process conforms to good manufacturing practice (Ref. 1). In addition to specification limits for lead, arsenic, mercury, and cadmium, we are requiring a specification for the minimum purity of soy leghemoglobin protein as a percent of the total protein in the color additive.

We have previously considered the safety of soy leghemoglobin preparation as the result of a submission from Impossible Foods who made its own determination, to which we had no questions, that the use of soy leghemoglobin preparation to optimize flavor in ground beef

analogue products intended to be cooked is generally recognized as safe (GRAS). Under section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(s)), a substance is GRAS if it is generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food before January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use. Under section 201(s) of the FD&C Act, a substance that is GRAS for a particular use in food is not a food additive and may lawfully be utilized for that use without our review and approval. There is no GRAS exemption, however, to the definition of a color additive in section 201(t) of the FD&C Act. Therefore, we must approve the use of a color additive in food before it is marketed; otherwise, the food containing the color additive is adulterated under section 402(c) of the FD&C Act (21 U.S.C. 342(c)).

A firm may voluntarily submit to FDA information supporting the firm's own conclusion that a substance is GRAS for its intended use in food through our GRAS notification program (see 81 FR 54960 (August 17, 2016)). Through this program, a GRAS notification (GRN) was submitted on behalf of Impossible Foods on October 3, 2017 (GRN 737). This GRN informed FDA that Impossible Foods concluded that the use of soy leghemoglobin preparation to deliver up to 0.8 percent soy leghemoglobin protein by weight in the final food was GRAS for optimizing flavor in ground beef analogue products intended to be cooked. Based on our evaluation of the information provided in GRN 737, as well as other available information, we issued a letter on July 23, 2018, to Impossible Foods stating that we had no questions regarding its conclusion that soy leghemoglobin preparation is GRAS for its intended conditions of use.

Importantly, in our response letter to Impossible Foods, we stated that because soy leghemoglobin preparation is reddish-brown, its use 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. In the case of the soy leghemoglobin preparation, the reddish color imparted to the uncooked ground beef analogue product is lost when the product is heated, and the soy leghemoglobin protein responsible for imparting the reddish color in the food is denatured by the cooking process. Impossible Foods' GRAS conclusion in GRN 737 was for the use of soy leghemoglobin preparation to optimize flavor in ground beef analogue products intended to be cooked. When soy leghemoglobin preparation is used in ground beef analogue products sold directly to consumers in an uncooked form, the reddish color imparted by the soy leghemoglobin preparation gives the appearance of uncooked ground beef to the ground beef analogue product. This specific use of soy leghemoglobin preparation to impart a reddish color to a food is important to the appearance and marketability of the food. Therefore, FDA determined that this use of soy leghemoglobin preparation requires premarket approval as a color additive (see § 70.3(g) (21 CFR 70.3(g))).

III. Safety Evaluation

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

As part of our safety evaluation to establish with reasonable certainty that a color additive is not harmful under its intended conditions of use, we consider the additive's manufacturing and

stability; the projected human dietary exposure to the additive and any impurities resulting from the petitioned use of the additive; the additive's toxicological data; and other relevant information (such as published literature) available to us.

IV. Safety of Petitioned Use of the Color Additive

A. *Exposure Estimate*

Soy leghemoglobin preparation is composed mainly of soy leghemoglobin protein, minor quantities of *P. pastoris* proteins, water, fat, carbohydrates, and any stabilizers that are used. During our safety review of this petition (CAP 9C0314), we evaluated the petitioner's dietary exposure estimates for the soy leghemoglobin preparation and for the soy leghemoglobin protein component of the preparation. To estimate dietary exposure, the petitioner used nationwide ground beef consumption data collected from 2003 to 2014 as part of the National Health and Nutrition Examination Survey and assumed a 1-to-1 substitution of conventional ground beef with ground beef analogue product containing soy leghemoglobin preparation at its maximum use level. The petitioner estimated the dietary exposure to soy leghemoglobin preparation for the U.S. population (aged 2 years or more) to be 3,556 milligrams/person/day (mg/p/d) at the mean and 7,911 mg/p/d at the 90th percentile. For soy leghemoglobin protein only, the estimated dietary exposure for the U.S population was 320 mg/p/d at the mean and 712 mg/p/d at the 90th percentile. FDA confirmed the petitioner's exposure estimates for soy leghemoglobin protein and soy leghemoglobin preparation and notes that the estimates assume that all conventional ground beef and ground beef-containing foods are replaced with ground beef analogue product (Ref. 1). FDA estimated the dietary exposure to total protein (soy leghemoglobin protein plus *P. pastoris* proteins) from the petitioned use of the color additive to be 871 mg/p/d (Ref. 1). We also considered U.S. consumers' dietary exposure to iron from the petitioned use of the color

additive and determined that no significant change in exposure to dietary iron would occur since the amount of iron from the petitioned use of soy leghemoglobin in ground beef analogue products is similar to the amount of iron found in traditional ground beef (Ref. 1).

B. Toxicological Considerations

To establish that soy leghemoglobin is safe for use as a color additive that provides up to 0.8 percent soy leghemoglobin protein in ground beef analogue products, the petitioner used a weight-of-evidence approach based on: (1) the history of consumption of soy, soy leghemoglobin protein, and *P. pastoris*; (2) the safety of *P. pastoris* as a production strain; (3) 14-day and 28-day feeding studies with soy leghemoglobin preparation in rats; (4) mutagenicity and genotoxicity studies of soy leghemoglobin preparation; and (5) an allergenicity assessment of soy leghemoglobin and *P. pastoris* proteins in the soy leghemoglobin preparation.

Based on our review of this petition (CAP 9C0314), we conclude that the proteins in the soy leghemoglobin preparation are well defined, non-toxic, and that the contribution of total proteins (soy leghemoglobin protein plus *P. pastoris* proteins) from the petitioned use of the color additive to total daily dietary protein would be only 1.7 percent, assuming a daily dietary intake of 50 grams of protein per person per day (Ref. 2). Regarding the *P. pastoris* strain developed by the petitioner for the production of soy leghemoglobin preparation, we conclude that it is non-toxicogenic and non-pathogenic. We evaluated the results from the 14-day dose range finding study and two 28-day toxicity studies in rats fed soy leghemoglobin preparation and conclude that they did not show any toxicologically relevant effects. We also determined that the mutagenicity and genotoxicity studies provided in the petition showed no evidence of mutagenic activity or increased chromosomal aberrations in cells exposed to soy leghemoglobin preparation.

To address the allergenicity potential of soy leghemoglobin preparation, the petition provided results from a study on the digestibility of soy leghemoglobin preparation, bioinformatic analyses of soy leghemoglobin protein and of *P. pastoris* proteins identified in the soy leghemoglobin preparation, and a memorandum from an expert in the field of food allergies on the potential allergenicity of soy leghemoglobin. We conclude that soy leghemoglobin and *P. pastoris* proteins in the soy leghemoglobin preparation are readily digested at acidic pH conditions found in the stomach and denatured at normal cooking temperatures. We also agree with the petitioner that the totality of evidence supports the conclusion that soy leghemoglobin protein and *P. pastoris* proteins present in soy leghemoglobin preparation do not pose risks of allergenicity when consumed, even for people who are allergic to foods containing soybean protein (Ref. 2).

V. Conclusion

Based on the data and information in the petition and other available relevant information, we conclude that the petitioned use of soy leghemoglobin as a color additive in ground beef analogue products is safe, provided the amount of soy leghemoglobin protein does not exceed 0.8 percent by weight of the uncooked product. We further conclude that this color additive will achieve its intended technical effect and is suitable for the petitioned use. Therefore, we are amending the color additive regulations in part 73 to provide for the safe use of this color additive as set forth in this document. In addition, based on the factors in 21 CFR 71.20(b), we conclude that batch certification of soy leghemoglobin is not necessary to protect the public health.

VI. Public Disclosure

In accordance with § 71.15(a) (21 CFR 71.15(a)), 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 ADDRESSES). As provided in § 71.15(b), we will delete from the documents any materials that are not available for public disclosure.

VII. Analysis of Environmental Impact

As stated in the December 13, 2018, *Federal Register* notice of filing, the petitioner claimed that this action is categorically excluded under § 25.32(k) (21 CFR 25.32(k)) because soy leghemoglobin would be added directly to food and is intended to remain in the food through ingestion by consumers and is not intended to replace macronutrients in food. We further stated that if FDA determines a categorical exclusion applies, neither an environmental assessment nor an environmental impact statement is required. We have not received any new information or comments regarding this claim of categorical exclusion. We have considered the petitioner's claim of categorical exclusion and have determined that this action is categorically excluded under § 25.32(k). Therefore, neither an environmental assessment nor an environmental impact statement is required.

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(l) of the FD&C 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(l) 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(l)(1) to (4) of the FD&C Act applies. In our review of this petition, we did not consider whether section 301(l) 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(l) 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(l) 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 are on display at 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>.

1. Memorandum from J. R. Srinivasan, Chemistry Review Team, Division of Food Ingredients (DFI), Office of Food Additive Safety (OFAS), Center for Food Safety and Applied Nutrition (CFSAN), FDA to E. Anderson, DFI, OFAS, CFSAN, FDA, June 20, 2019.

2. Memorandum from S. Choudhuri, Toxicology Review Team, DFI, OFAS, CFSAN, FDA to E. Anderson, DFI, OFAS, CFSAN, FDA, June 21, 2019.

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 the authority delegated to the Commissioner of the 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. Add § 73.520 to read as follows:

§ 73.520 Soy leghemoglobin.

(a) *Identity.* (1) The color additive soy leghemoglobin is a stabilized product of controlled fermentation of a non-pathogenic and non-toxicogenic strain of the yeast, *Pichia pastoris*, genetically engineered to express soy leghemoglobin protein. Soy leghemoglobin protein is the principal coloring component of the color additive and imparts a reddish-brown color.

(2) Color additive mixtures made with soy leghemoglobin may contain only those diluents that are suitable and are listed in this subpart as safe for use in color additive mixtures for coloring foods.

(b) *Specifications.* Soy leghemoglobin shall conform to the following specifications and shall be free from impurities, other than those named, to the extent that such impurities may be avoided by good manufacturing practice:

(1) Soy leghemoglobin protein purity on protein basis (weight/weight), not less than 65 percent, as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

(2) Lead, not more than 0.4 milligrams per kilogram (mg/kg) (0.4 parts per million (ppm)).

(3) Arsenic, not more than 0.05 mg/kg (0.05 ppm).

(4) Mercury, not more than 0.05 mg/kg (0.05 ppm).

(5) Cadmium, not more than 0.2 mg/kg (0.2 ppm).

(c) *Uses and restrictions.* Soy leghemoglobin may be safely used in ground beef analogue products such that the amount of soy leghemoglobin protein does not exceed 0.8 percent by weight of the uncooked ground beef analogue product.

(d) *Labeling.* The label of the color additive and of any mixture prepared therefrom intended solely or in part for coloring purposes must conform to § 70.25 of this chapter.

(e) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification requirements of section 721(c) of the Federal Food, Drug, and Cosmetic Act.

Dated: July 26, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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