No. 20-70747

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

CENTER FOR FOOD SAFETY,

Petitioner,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al*.,

Respondents,

and

IMPOSSIBLE FOODS INC.,

Intervenor-Respondent.

ON PETITION FOR REVIEW FROM THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

PETITIONER'S OPENING BRIEF

CENTER FOR FOOD SAFETY
Ryan D. Talbott
Sylvia Shih-Yau Wu
2009 NE Alberta St., Suite 207
Portland, OR 97211
T: (971) 271-7372
rdtalbott@centerforfoodsafety.org
swu@centerforfoodsafety.org

CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1, Petitioner Center for Food Safety certifies that it has no parent corporation and that no publicly held corporation owns more than ten percent of the Petitioner.

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JURISDICTIONAL STATEMENT

This petition seeks review of the December 19, 2019 decision by the United States Food and Drug Administration (FDA) to deny Petitioner Center for Food Safety's (CFS) objections to the agency's approval of genetically engineered (GE) soy leghemoglobin as a color additive for use in Intervenor Impossible Foods Inc.'s (Impossible Foods) "plant-based or other non-animal derived ground beef-like food products." Excerpts of Record (ER) ER001-007 ("Listing of Color Additives Exempt From Certification; Soy Leghemoglobin"); 143-46. This Court has jurisdiction under the Federal Food, Drug and Cosmetic Act (FFDCA), which provides:

> In a case of actual controversy as to the validity of any order under [21 U.S.C. § 371(e)], any person who will be adversely affected by such order if placed in effect at any time prior to the ninetieth day after such order is issued file a petition with the United States court of appeals for the circuit wherein such person resides or has his principal place of business, for a judicial review of such order.

21 U.S.C. § 371(f)(1).[1] "The provisions of section 371(e), (f), and (g) of this title shall . . . apply to and in all respects govern proceedings for the

[1] *Pactra Industries, Inc. v. Consumer Prod. Safety Comm'n*, 555 F.2d 677, 679 (9th Cir. 1977); *Consumer Fed'n of Am. v. U.S. Consumer Prod. Safety Comm'n*, 883 F.2d 1073, 1076 (D.C. Cir. 1989).

issuance, amendment, or repeal of [color additive] regulations under subsection (b) or (c) of this section (including judicial review of the Secretary's action in such proceedings[.]" 21 U.S.C. § 379e(d). Petitioner Center for Food Safety (CFS or Petitioner) timely filed this petition for review. 21 U.S.C. § 371(f)(1); 21 C.F.R. § 10.45.

Petitioner has standing. An individual has Article III standing if he or she is under threat of suffering an injury-in-fact that is concrete and particularized; the threat must be actual and imminent, not conjectural or hypothetical; it must be fairly traceable to the challenged action of the respondent; and it must be likely that a favorable judicial decision will prevent or redress the injury. *Friends of the Earth, Inc. v. Laidlaw Envtl. Servs. (TOC), Inc.*, 528 U.S. 167, 180-81 (2000). A public interest organization like Petitioner in turn has representational standing "when: (a) its members would otherwise have standing to sue in their own right; (b) the interests it seeks to protect are germane to the organization's purpose; and (c) neither the claim asserted nor the relief requested requires the participation of individual members in the lawsuit." *Hunt v. Wash. State Apple Advert. Comm'n*, 432 U.S. 333, 343 (1977). FDA's challenged action has directly injured and constitutes a

continuing threat of injury to Petitioner's members' health and safety interests. Maker Decl. ¶¶ 2-11; Kelley Decl. ¶¶ 2-13; Kaluza Decl. ¶¶ 2-11; Thomas Decl. ¶¶ 2-11.

One member, Janet Maker, is in remission from breast cancer, and her diet does not allow any meat or dairy. Maker Decl. ¶ 4. Although Ms. Maker strives to purchase organically-grown, non-GE foods, she decided to make a limited exception and try the Impossible Burger when it was introduced to grocery stores. *Id.* ¶ 5. Despite not eating meat, Ms. Maker still enjoys the taste of beef, and the Impossible Burger provided a meat-alternative with "meat-like texture and taste." *Id.* However, after learning more about how Impossible Burgers are produced with GE technology and FDA's flawed safety review of soy leghemoglobin, Ms. Maker is concerned about the safety of this GE substance. In particular, Ms. Maker is concerned about increased globulin values detected in some rats that were fed soy leghemoglobin during a 28 day-feeding study conducted by Impossible Foods. *Id.* ¶ 7-10.

Another member, M'Lisa Kelley, has purchased the Impossible Burger at retail both for personal use at home and for her school

district, where she teaches culinary arts and is the Director of Nutrition. Kelley Decl. ¶¶ 3, 6-7. When Ms. Kelley purchased Impossible Foods' products, she did not know that they contained GE soy leghemoglobin. *Id.* ¶ 8. When Ms. Kelley did learn that Impossible Foods' products contain GE soy leghemoglobin, she pulled the products from her school district and stopped buying it for home use. *Id.* After learning more about products like the Impossible Burger that are made with GE ingredients, Ms. Kelley is concerned about the safety of this and other products containing soy leghemoglobin and angered at the lack of transparency in FDA's safety review. *Id.* ¶ 12-13.

These and the other declarations demonstrate that FDA's challenged action has directly injured and constitutes a continuing threat of injury to Petitioner's members' health and safety interests.

Finally, Venue is proper because Petitioner resides within this Circuit. *See* Hanson Decl. ¶ 2.

ISSUES PRESENTED

1. Whether FDA violated the FFDCA in approving soy leghemoglobin, a novel GE substance derived from the roots of soybeans that has never before been used in food, as a *color additive* without making the requisite determination that there is "convincing evidence that establishes with reasonable certainty that no harm will

result" from its intended use, and instead applying a more relaxed standard applicable only to *food additives* and which does not require "convincing evidence";[2]

2. Whether FDA violated the FFDCA in approving soy leghemoglobin as a color additive despite lacking substantial evidence supporting its decision, when FDA itself repeatedly questioned the safety of this GE substance in an earlier separate review and because it made its decision without long-term animal toxicity studies even though short-term studies resulted in observed health effects in test animals.

STATEMENT OF THE CASE

This case is about whether FDA ensured that food containing novel substances that have never been consumed by humans are safe to eat before being sold in grocery stores across the country. At issue is the genetically engineered (GE) substance Intervenor Impossible Foods developed, "soy leghemoglobin," which is used to impart a reddish-brown coloring in Intervenor's GE meat alternative products, like the "Impossible Burger." ER143-144; 300. The questions presented in this case are important because, as FDA has stated, "there is no history or

[2] Food additives and color additives are distinct and regulated under separate parts of the FFDCA. *See* 21 U.S.C. §§ 348 (food additives) and 379e (color additives). FDA regulations for food additives are in 21 C.F.R. Part 170 and its color additives regulations are in 21 C.F.R. Part 70. There is no dispute here that what is at issue is a color additive. ER143.

knowledge of human dietary exposure to soy leghemoglobin from [soybean] roots." ER081. Stated differently, this case is about FDA's safety review of a novel, new product, produced in a new, novel mechanism that has no history of safe human health use.

Despite the novelty of this substance, in 2018, Impossible Foods petitioned FDA to amend the color additive regulations to provide for the purported safe use of soy leghemoglobin as a color additive. ER303. On August 1, 2019, FDA agreed to do so, issuing a final rule so amending its color additive regulations. ER143. CFS filed timely objections, which FDA denied. ER001. CFS timely filed a petition for review in this Court.

I. HOW IMPOSSIBLE FOODS' GENETIC MANIPULATION CAUSED A NEVER-BEFORE-CONSUMED PROTEIN TO GET ON THE SHELVES OF GROCERY STORES.

The color additive at issue here, soy leghemoglobin, is an artificially generated hemeprotein found in the roots of soybeans, a leguminous plant. ER290. Hemeproteins are found in both plants and animals, and include hemoglobin, myoglobin, and leghemoglobin. Hemoglobin is present in the red blood cells of animals while myoglobin is present in the muscles of animals. Leghemoglobin is present in the

root nodules of leguminous plants, like soybeans. All three of these hemeproteins appear red in color.

Although proteins are a part of the human food supply, "not all proteins are safe." ER081. And while there may be history of safe use of soy proteins from other parts of the soybean plant in some instances, "there is no history or knowledge of human dietary exposure to soy leghemoglobin from [soybean] *roots*." ER081 (emphasis added). Indeed, extra caution is called for when the protein is derived from a "major food allergen," and "soybeans are identified as a major food allergen." ER004. It is critical then that before the soy leghemoglobin color additive at issue in this case is added to foods offered in grocery stores throughout the country, that FDA have convincing evidence ensuring this new substance is in fact safe. That emphatically did not happen here.

First, it is necessary to explain how the soy leghemoglobin found in the roots of soybeans became the color additive at issue in this case. When Impossible Foods started out, it discovered that the hemeproteins

discussed above are "what makes meat taste so meaty."[3] In order to make a "meaty" burger without the meat, Impossible Foods decided to use soy leghemoglobin.[4] When added to ground beef analogue products, soy leghemoglobin preparation imparts a reddish-brown color, giving the appearance of uncooked ground beef. Impossible Foods sought color additive approval for soy leghemoglobin preparation to enhance the "appearance and marketability" of uncooked products sold directly to consumers. ER144.

Initially, Impossible Foods "harvest[ed] leghemoglobin directly from the roots of soy plants."[5] However, the company realized that, in order for it to produce enough soy leghemoglobin at the industrial scale needed to mass produce its meatless burgers, it could not continue to

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[3] Impossible Foods, *FAQ: What is Soy Leghemoglobin, or Heme?*, https://faq.impossiblefoods.com/hc/en-us/articles/360019100553-What-is-soy-leghemoglobin-or-heme- (last visited Aug. 17, 2020).

[4] Impossible Foods, *FAQ: What is Soy Leghemoglobin, or Heme?*, https://faq.impossiblefoods.com/hc/en-us/articles/360019100553-What-is-soy-leghemoglobin-or-heme- (last visited Aug. 17, 2020).

[5] Impossible Foods, *FAQ: How Do You Make Heme?*, https://faq.impossiblefoods.com/hc/en-us/articles/360034767354 (last visited Aug. 17, 2020).

just extract soy leghemoglobin directly from the roots of soybeans.[6] Impossible Foods, therefore, turned to synthetic biology—"genetic engineering on steroids"[7]— to artificially create the amount of soy leghemoglobin necessary to give Impossible Foods' meatless burgers their meat-like color.

Unlike genetic engineering alone, which "was a cut and paste affair, in which biotechnologists shuffled pieces of DNA . . . between already existing species," synthetic biology is "the design and construction of *new* biological parts, devices and systems that *do not exist in the natural world* and also the redesign of existing biological systems to perform specific tasks."[8] This aggressive form of genetic engineering operates "in a 'Wild West' free-for-all environment with

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[6] *Id.*

[7] ETC Group, *Extreme Genetic Engineering: An Introduction to Synthetic Biology* 1 (Jan. 2007), *report available for download at* https://www.etcgroup.org/content/extreme-genetic-engineering-introduction-synthetic-biology (last visited Aug. 17, 2020).

[8] ETC Group, *Extreme Genetic Engineering: An Introduction to Synthetic Biology* 1, 3 (Jan. 2007), *report available for download at* https://www.etcgroup.org/content/extreme-genetic-engineering-introduction-synthetic-biology (last visited Aug. 17, 2020). (underline emphasis in original; italics added).

virtually no regulatory oversight."[9] It is through this extreme form of genetic engineering that Impossible Foods creates its meatless products.

The soy leghemoglobin at issue here is a "preparation" composed of the soy leghemoglobin protein[10] found in soybean roots and a yeast, *Pichia pastoris* (*P. pastoris*). ER290-91. Through genetic engineering, Impossible Foods extracts the gene containing leghemoglobin protein from the roots of soybeans and inserts it into the *P. pastoris* yeast. The *P. pastoris* yeast is constructed to overexpress, through fermentation in giant vats, *P. pastoris* enzymes that catalyze heme B biosynthesis and to express leghemoglobin. Following fermentation, the color additive (soy leghemoglobin preparation) is isolated from the fermented yeast and stored either as a frozen liquid or in a spray dried form. ER292-93. This mass production of soy leghemoglobin concentrate is then added to Impossible Foods' meatless products in order to give them their meat-like texture and taste. Because the final "soy leghemoglobin

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[9] *Id.* at 4.

[10] "Soy leghemoglobin protein, the principle coloring component in the color additive, comprises mainly of two components, leghemoglobin C2, and a heme cofactor (heme B)." ER290.

preparation" imparts a reddish color to Impossible Foods' products, it needed FDA's approval as a color additive, which it obtained. ER143-46.

This case centers on whether FDA satisfied its statutory and regulatory duties in reviewing and approving soy leghemoglobin as a color additive. This case is *not* about whether Impossible Foods' GE products are part of a meaningful remedy to the ills of factory farming or the benefits of a plant-based diet. Those are policy debates that have nothing to do with this case. This case is about whether FDA followed the law when it approved this novel color additive. It did not.

II. FDA REGULATION OF FOOD AND COLOR ADDITIVES.

There are several distinct routes through which substances can be added to our food supply. One route is as a food additive, not at issue here. A second route is if the use of a substance is generally recognized as safe (GRAS) and, therefore, exempt from the definition of food additive, also not at issue here. A third route is as a color additive, which is at issue here. This case is about FDA's approval of soy leghemoglobin as a color additive for use in Impossible Foods' genetically-engineered soy-based burgers sold as a raw product at retail.

However, in order to understand each regulatory pathway, and because Impossible Foods has also self-certified that soy leghemoglobin is "GRAS" for use in the same meatless burgers that are sold as a cooked product in restaurants, it is helpful to consider each of these distinct routes in some detail.

Food Additives

The FFDCA requires FDA to "protect the public health by ensuring that . . . foods are safe." 21 U.S.C. § 393(b)(2)(A). In 1958, concerned about the increased number of chemicals entering the food supply, Congress amended the FFDCA to "prohibit the use in food of additives which have not been adequately tested to establish their safety." Food Additives Amendment of 1958, Pub. L. No. 85-929, 72 Stat. 1784, 1784 (Sept. 6, 1958). Under the Food Additives Amendment, a food additive is "any substance the intended use of which results . . . in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not [GRAS]." 21 U.S.C. § 321(s). A food additive is presumed "unsafe" unless it is used "in conformity with[] a regulation . . . prescribing the conditions under which such additive may be safely used." 21 U.S.C. § 348(a)(2).

In determining whether the intended use of a food additive is safe, FDA must consider, *inter alia*, the "probable consumption of the additive" and the "cumulative effect of the additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet." 21 U.S.C. § 348(c)(5)(A)-(B). For food additives, FDA regulations define "safe" to mean "there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use." 21 C.F.R. § 170.3(i). That is, the safety test for food additives is a "reasonable certainty" test.

GRAS Substances

In what was supposed to be a minor exception to the premarket food additive regulatory process—but has increasingly become the dominant pathway[11] by far—is GRAS substances. A substance is GRAS if it is "generally recognized, among experts qualified by scientific

[11] *See* ER084 (2011 study "estimated that more than 10,000 additives are allowed in food, 43% of which are GRAS" substances); *see also*, Gov't Accountability Office, *Food Safety: FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS)*, 2010 (hereafter GAO Report), https://www.gao.gov/products/GAO-10-246.

training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe[.]" 21 U.S.C. § 321(s). In 1997, FDA issued a proposed rule to implement the GRAS exception, opening up the loophole further, and directed food manufacturers to begin complying with the rule. *See* 62 Fed. Reg. 18,938 (Apr. 17 1997). FDA then never finalized the rule or responded to opposed public comment on it for nearly twenty years, before litigation compelled FDA to issue the final GRAS rule in 2016. *See Ctr. for Food Safety v. Burwell*, No. 14-cv-00267-RC (D.D.C. Oct. 20, 2014), ECF No. 15 (consent decree establishing final rule deadline); 81 Fed. Reg. 54,960 (Aug. 17, 2016).

After issuance of the final GRAS rule, CFS and other consumer public interest organizations challenged the final rule itself, for failing to comply with the FFDCA or the Administrative Procedure Act and for failing to protect public health and provide transparency for food additives and GRAS substances. *See Ctr. for Food Safety v. Price*, No. 17-cv-3833 (VSB), 2018 WL 4356730 (S.D.N.Y. Sept. 12, 2018), ECF No. 44 (order denying motion to dismiss as to CFS and another public interest consumer group). While that litigation is pending and unless

the court holds the final rule unlawful, under the final GRAS rule, food manufacturers are permitted to self-determine, in secret, that novel chemical substance are GRAS, without any notice to FDA or the public. In such circumstances, the safety of potential food additives are determined solely by the food manufacturer, without any input or even review from FDA, the agency charged with ensuring our food is safe. Under this secret GRAS system, the public is prevented from knowing whether the food they eat contains substances that have been adequately tested for safety.

Even when a food manufacturer chooses to notify FDA of its GRAS determination, this *voluntary* notification process is mired in conflicts of interest and does not provide sufficient oversight of GRAS substances added to food. *See* ER083-087; GAO Report. For example, the final GRAS rule only provides that, upon receipt of a manufacturer's GRAS notice, FDA will respond by letter indicating whether it has any questions about the manufacturer's conclusion that its own chemical substance is GRAS for a particular use. *See* 21 C.F.R. § 170.265. Importantly, if FDA does not question a manufacturer's conclusion, in which it issues a "no questions" letter, the agency is *not* affirmatively

agreeing that the chemical substance is indeed safe for human consumption or undertaking any of its own review for safety; it is merely not disagreeing with the manufacturer's conclusion about its own product. *See* 81 Fed. Reg. at 55,014-15.

Color Additives

Shortly after enacting the Food Additives Amendment in 1958, Congress enacted the Color Additives Amendment in 1960. Pub. L. No. 86-618, 74 Stat. 397 (July 12, 1960). Under the Color Additives Amendment, a "color additive" is "a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived . . . and . . . when added or applied to a food . . . is capable (alone or through reaction with other substance) of imparting color thereto[.]" 21 U.S.C. § 321(t)(1). A color additive "shall . . . be deemed unsafe" unless "there is in effect, and such additive and such use are in conformity with, a regulation[.]" 21 U.S.C. § 379e(a)(1). Congress tasked FDA with issuing such regulations.

Both the structure and the legislative history of the Color Additives Amendment indicate with unmistakable clarity Congress's intent to subject color additives to greater scrutiny than food additives.

One of the principal sponsors of the Color Additives Amendment explained the distinction between food and color additives and why Congress ultimately decided to subject the latter to heightened scrutiny:

> I can say that in this matter of color additives there is every reason why we should have a strong bill. Some food additives serve a useful purpose. They have helped to develop and improve our food supply in many ways. However, *color additives provide no nutrient value. They have no value at all, except so-called eye appeal. We should be particularly careful with them, therefore. They add nothing in any other way*.

Color Additives Amendment of 1960: Hearings on H.R. 7624 and S. 2197 Before the H. Comm. on Interstate and Foreign Commerce, 86th Cong., 2d Sess. 108 (1960) (statement of Rep. James Delaney of New York) (emphasis added).[12] This institutional caution to be "particularly careful" with color additives was built into the structure of the Color

[12] So central was Rep. Delaney's involvement in both the Food Additive and Color Additive Amendments that a clause in each statute prohibiting the approval of an additive that is found to induce cancer are commonly referred to as the "Delaney Clause." *See* 21 U.S.C. § 348(c)(3) (food additives) *and* 21 U.S.C. § 379e(b)(5)(B) (color additives); *see also*, U.S. Dep't of Agric., *What is the Delaney Clause?*, https://ask.usda.gov/s/article/What-is-the-Delaney-Clause#:~:text=The%20Food%20Additives%20Amendment%20and,of%20food%20additives%2C%20to%20induce (last visited Aug. 17, 2020).

Additives Amendment itself and regulations promulgating that amendment.

For example, unlike for food additives, there is no GRAS exemption for color additives. *Compare* 21 U.S.C. § 321(s) (food additives), *with* 21 U.S.C. § 321(t) (color additives).[13] Thus, any potential color additive must undergo a premarket safety review that is separate and apart from the food additive/GRAS review, with its own safety determination. As part of that process, color additives must be affirmatively approved by FDA before the color additive can be added to food and sold to consumers.

FDA's regulations further Congress's "particularly careful" approach to color additives. In making the color additive safety determination, FDA considers, *inter alia*, "the probable consumption of, or relevant exposure from, the additive" and "the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or

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[13] *See also*, FDA, *Color Additives History*, https://www.fda.gov/industry/color-additives/color-additives-history#:~:text=Even%20though%20DHA%20is%20colorless,definition%20of%20a%20color%20additive (last visited Aug. 17, 2020).

substances in such diet." 21 U.S.C. § 379e(b)(5)(A). Crucially, unlike FDA's "reasonable certainty" definition of "safe" for food additives, the agency's definition of "safe" for color additives requires that there is "*convincing evidence* that establishes with reasonable certainty that no harm will result from the intended use of the color additive." 21 C.F.R. § 70.3(i) (emphasis added); *cf.* 21 C.F.R. § 170.3(i) (food additive is safe so long as "there is a *reasonable certainty* in the minds of competent scientists that the substance is not harmful under the conditions of its intended use.") (emphasis added). FDA's use of a heightened "convincing evidence" standard for color additives advances Congress's intent that color additives be treated "particularly careful[ly]" and separate from food additives.

III. IMPOSSIBLE FOODS' FIRST GRAS NOTICE.

Of the three distinct routes described above, Impossible Foods first attempted the GRAS route to begin offering its GE burgers for sale in restaurants where they would be cooked and sold to consumers. In September 2014, Impossible Foods notified FDA of its self-determination asserting that soybean leghemoglobin is GRAS for use in

the company's GE meatless products. ER079. FDA designated this GRAS notice as GRN 540. ER079.

In April 2015, FDA raised concerns about Impossible Foods' safety assessment of soy leghemoglobin. ER081-82. For example, FDA stated that:

> Although proteins are a part of the human food supply, not all proteins are safe. Information [provided by Impossible Foods in GRN 540] *addressing the safe use of modified soy protein does not adequately address safe use of soybean leghemoglobin protein* from the **roots** of the soybean plant in food.
>
> [. . .]
>
> The dietary exposure discussion in GRN 540 includes history of safe use of soy proteins from the soybean plant in general and does not discuss soy leghemoglobin from the roots of the soybean plant, which is the ingredient described in the GRAS notice. The discussion is not relevant in the context of the GRAS notice because *soybean root is not a commonly consumed human food*. Please provide relevant information, as there is no history or knowledge of human dietary exposure to soy leghemoglobin from roots [of soybean plants].

ER081 (bold emphasis in original, italics added).

In May 2015, Impossible Foods responded, claiming that although "the [soy leghemoglobin] protein is isolated from the root nodule, it is substantially similar to proteins consumed daily by the global population, in the form of meat and other vegetables" and "there is no

evidence to suggest that soy leghemoglobin in food will behave any differently from the myriad other functionally equivalent and widely consumed globin proteins in the human diet." ER021, 023.

Despite Impossible Foods' continued claims that soy leghemoglobin was safe, in August 2015, FDA rejected those claims, explaining that Impossible Foods' arguments "individually and collectively, do not establish the safety of [soy leghemoglobin] for consumption, nor do they point to a general recognition of safety[.]" ER045. In particular, FDA found that:

- Conformational similarity or functional similarity among proteins is not an indication of the safety of proteins for consumption.
- Just belonging to the globin family does not guarantee that the protein will be safe to consume.
- Binding oxygen and other similar molecules (CO, NO) is the function of all respiratory proteins. Such function has nothing to do with the safety of the proteins for consumption.
- Analyses using other software . . . indicate that [soy leghemoglobin] could be an allergen.
- [T]he list of proteins (~20-25% of the final product) co-purified with the [soy leghemoglobin] raises further question on how the safety argument could be made based solely on SLH.

ER045-46. Recognizing that it lacked sufficient evidence to demonstrate that its novel soy leghemoglobin is GRAS, on November 10, 2015, Impossible Foods notified FDA that it was withdrawing its GRAS notice

and explained that it would submit another GRAS notice in the future, with additional supportive information. ER047.

IV. IMPOSSIBLE FOODS' SECOND GRAS NOTICE.

Two months after withdrawing its GRAS notice, Impossible Foods requested a meeting with FDA to discuss filing a second GRAS notice for soy leghemoglobin. ER048-53. In particular, the company was interested in knowing whether FDA would agree to a 90-day oral feeding study in rats to assess the systemic toxicology of soy leghemoglobin at doses of 125, 250, and 500 mg/kg/day in a sample of 10 animals/sex. ER049. In February 2016, that meeting was held. ER072-73. During the meeting, FDA "provided feedback on the toxicology aspects of a safety study used to support a conclusion of GRAS status" and, again, stressed the fact that soy leghemoglobin is "an ingredient that *has not been used in food before*." ER072-73 (emphasis added).

In August 2016, Impossible Foods sent a letter to FDA regarding the design of safety studies for soy leghemoglobin. ER074. Impossible Foods explained that while it had originally planned to "complete a 90-day feeding study in rodents, . . . [a]fter consideration of the Agency's feedback during the [Feb. 2016] meeting, Impossible Foods has decided

to conduct a 28-day study" instead of a 90-day study, with "doses of 250, 500, and 750 mg/kg bw/day." ER074. Impossible Foods wanted FDA to confirm "that this dose schedule is acceptable, and would support the safety of the product *in a future GRAS notification*." ER074 (emphasis added). In September 2016, FDA responded:

> It is necessary to emphasize that we cannot provide confirmation that a study – which has not yet been conducted – will support the safety of a product in a GRAS conclusion. We cannot offer such assurances in advance of the conduct of the study. As you are aware, the safety assessment supporting a GRAS conclusion involves multiple types of information, not just a feeding study . . . The support of one dosing study cannot be assessed independently of the other types of information . . . In regards to the time frame of the study, we do not provide specific suggestions such as this *to a notifier for a GRAS notice*.

ER075 (emphasis added).

One year later, in October 2017, Impossible Foods submitted a second GRAS notice for soy leghemoglobin, which FDA designated as GRN 737. ER144. In support of its second GRAS notice, Impossible Foods included the results of a rat-feeding study it commissioned, claiming it was designed and conducted in accordance with Chapter

IV.C.4.a. of FDA's Redbook.[14] ER311; ER277. This chapter directs food manufacturers to conduct rat-feeding studies "with *at least* 20 rodents per sex per group" for "a *minimum* of 90 consecutive days" to assess the sub-chronic effects of the test substance, here soy leghemoglobin. ER268; 270 (emphasis added). However, the rat-feeding study Impossible Foods commissioned included just *ten* rats per sex per group and was only conducted for *28 days*. ER311-312.

Despite the fact that Impossible Foods' rat-feeding study did not come anywhere close to meeting the minimum requirements for a sub-chronic toxicity study, in July 2018, FDA, which to this point had been skeptical about the safety of soy leghemoglobin, then said that it had "no questions" about the company's self-determined GRAS status for soy

[14] The Redbook is FDA's guidance that provides direction to food manufacturers regarding the design of toxicological studies for assessing the safety of food additives, color additives, and, when appropriate, GRAS substances. ER151.

leghemoglobin.[15] ER144. As explained above, this "no questions" letter only conveyed Impossible Foods'—*not FDA's*—safety assurances.[16]

Although FDA had no questions as to Impossible Foods' *GRAS determination*, the agency explained that because "soy leghemoglobin preparation is reddish-brown, its use may constitute a color additive use." ER144. FDA further explained that its "no questions" letter was "*not* an approval for use [of soy leghemoglobin] *as a color additive*." *See* FDA No Questions Letter at 4-5 (emphases added). In other words, if Impossible Foods wanted to sell *uncooked* Impossible Burgers containing soy leghemoglobin directly to consumers in grocery stores, it would need FDA's approval as to the safety of soy leghemoglobin as a color additive. So Impossible Foods filed a color additive petition. ER305-319.

V. IMPOSSIBLE FOODS' COLOR ADDITIVE PETITION.

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[15] Upon receiving FDA's "no questions" letter, Impossible Foods began marketing Impossible Burgers containing soy leghemoglobin to restaurants where it could be sold as a *cooked* product to consumers. ER300.

[16] *See* FDA No Questions Letter at 5 (July 23, 2018) ("[t]his letter is not an affirmation [by FDA] that soy leghemoglobin is GRAS"), *available at* https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=737 (click on "FDA has no questions" link) (last visited Aug. 17, 2020).

In November 2018, Impossible Foods submitted a petition to FDA proposing soy leghemoglobin as a color additive in the company's GE meat alternative products intended to be sold at retail as an uncooked product. ER303-04. Instead of supporting its petition with additional testing designed to meet the safety standard for a *color additive*, Impossible Foods resubmitted the 28-day rat feeding study that it commissioned in support of its earlier *GRAS notice*. In August 2019, FDA published a final rule adding soy leghemoglobin as a color additive safe for human consumption. ER143-46. CFS timely filed objections to FDA's safety determination and requested an evidentiary hearing. ER008.

CFS explained how FDA's final rule failed to apply the correct standard of safety for color additives: "*convincing evidence* that establishes with reasonable certainty that no harm will result from the intended use of the color additive." 21 C.F.R. § 70.3(i) (emphasis added). Further, FDA should have required Impossible Foods to conduct longer subchronic (minimum *90 days*) and chronic (minimum *one year*) toxicity studies, which is what the agency's guidelines specify for color additives, as opposed to the 28-day study the company conducted. On

December 19, 2019, FDA denied CFS's objections and request for an evidentiary hearing. ER001-07. CFS then commenced this case.

SUMMARY OF ARGUMENT

This case is about FDA's fundamental duty to ensure that our food is safe, and specifically its failure to comply with core legal safety mandates before it approved a new color additive, for a novel new type of food eaten for the first time. FDA used an erroneous, lower legal standard, and failed to support its decision with substantial evidence.

First, in approving Impossible Foods' petition and issuing the final rule, FDA applied an incorrect, lower safety standard than required by its own color additive regulations. This violated the FFDCA. Under the FFDCA, a color additive is presumed *unsafe*. 21 U.S.C. § 379e(a). To overcome this presumption, a petitioner must supply data to FDA establishing that the use of the color additive will be safe. 21 U.S.C. § 379e(b)(4). FDA has promulgated regulations for safety evaluations of color additives. *See* 21 C.F.R. Part 70.

Vitally, unlike food additives and GRAS substances, FDA's color additive regulations require "*convincing evidence* that establishes with reasonable certainty that no harm will result from the intended use of

the color additive." 21 C.F.R. § 70.3(i) (emphasis added). In denying CFS's objections, FDA entirely omitted the "convincing evidence" test from the standard it applied, equating the safety for color additives with that of food additives and GRAS substances. ER004. By so doing, FDA based its approval of soy leghemoglobin on an incorrect, lower safety standard.

Second, FDA's approval of soy leghemoglobin lacks substantial evidence in the record, also violating the FFDCA. The approval lacked critical toxicity studies required by FDA's own guidelines, and the inadequate studies that FDA *did* review also showed statistically significant toxicological effects in the tested animals.

FDA guidelines provide specific toxicity studies to evaluate the safety of color additives. Those guidelines require Impossible Foods to conduct a subchronic toxicity study and a chronic toxicity study with rodents as part of FDA's color additive safety review. Impossible Foods claims that it conducted a subchronic toxicity study with rodents in accordance with the appropriate guidelines, which require that a minimum of 20 rodents per sex per group are fed the test substance for a minimum of 90 days. But Impossible Foods' study, conducted in

support of its second GRAS notice, *not* its color additive petition, only contained *ten* rodents per sex per group and was only conducted for *28* days. Despite not meeting the minimum requirements for a subchronic toxicity study, FDA relied on this study to support its decision approving soy leghemoglobin as a color additive.

Moreover, even though Impossible Foods' 28-day study did not comply with the minimum requirements for sub-chronic toxicity studies, it still resulted in statistically significant toxicological effects in some rats that should have triggered further testing for longer periods of time and with the appropriate number of test animals. However, FDA discounted these observed effects stating that because the changes did not occur in both sexes, they were insignificant. There is no basis for this rationale in FDA's toxicity study guidelines.

By declining to require a subchronic toxicity study and chronic toxicity study that met the minimum requirements set out in its guidance for a color additive for which "there is no history or knowledge of human dietary exposure," ER081, and relying on factors that are not supported in its guidance to discount statistically significant

toxicological effects, FDA lacked substantial evidence to conclude that soy leghemoglobin is safe for its intended use.

For either and both of these reasons, the final rule therefore must be vacated.

STANDARD OF REVIEW

The Court may sustain FDA's decision under the FFDCA only "if supported by substantial evidence[.]" 21 U.S.C. § 371(f)(3). First, "the substantiality of evidence must take into account whatever in the record fairly detracts from its weight. This is clearly the significance of the requirement . . . that courts consider the whole record." *Universal Camera Corp. v. Nat'l Labor Relations Bd.*, 340 U.S. 474, 488 (1951). Second, judicial review must be "searching and careful, subjecting the agency's decision to close judicial scrutiny." *Containerfreight Corp. v. United States*, 752 F.2d 419, 422 (9th Cir. 1985) (internal citations and quotations omitted). Third, the agency's action may be upheld only "on the basis articulated by the agency itself." *Nat'l Family Farm Coal. v. U.S. E.P.A.*, 960 F.3d 1120, 1133 (9th Cir. 2020) (quoting *Nat. Res. Def. Council v. U.S. E.P.A.*, 735 F.3d 873, 877 (9th Cir. 2013)). Fourth, "[t]he substantial evidence standard affords an agency less deference than the

arbitrary and capricious standard." *Pollinator Stewardship Council v. U.S. E.P.A.*, 806 F.3d 520, 533 (9th Cir. 2015) (N.R. Smith, J., concurring) (citing *Universal Camera Corp.*, 340 U.S. at 477; *Union Oil Co. of Cal. v. Fed. Power Comm'n*, 542 F.2d 1036, 1040-41 (9th Cir. 1976)). That is, if FDA's decision is arbitrary and capricious, it also cannot be supported by substantial evidence. To avoid being arbitrary and capricious, FDA "must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (internal citations and quotations omitted). The Court's "review must not rubber-stamp . . . administrative decisions that [the court deems] inconsistent with a statutory mandate or that frustrate the congressional policy underlying a statute." *Ocean Advocates v. U.S. Army Corps of Eng'rs*, 361 F.3d 1108, 1119 (9th Cir. 2004) (internal citations and quotations omitted). Any difference between these two standards of review is immaterial here because FDA's decision satisfies neither. Finally, if this Court concludes that FDA's action violated the

FFDCA, this Court should set aside, or vacate, the decision. *Pollinator Stewardship*, 806 F.3d at 532-33.

ARGUMENT

I. FDA FAILED TO APPLY THE CONVINCING EVIDENCE STANDARD TO IMPOSSIBLE FOODS' COLOR ADDITIVE PETITION.

In denying CFS's objections and approving soy leghemoglobin as a color additive, FDA conflated the standard of safety for *color additives* with the standard of safety for *food additives and GRAS substances*. While FDA acknowledged that the regulatory programs for color additives, food additives, and GRAS substances "are distinct," the agency nevertheless insisted that the standard of safety for each program "is the same." ER004. FDA is wrong.

A. The structure of the Color Additives Amendment shows Congress intended to subject color additives to greater scrutiny than food additives.

Congress intended FDA to subject color additives to greater scrutiny than food additives. This is reflected by the fact that when Congress enacted the Color Additives Amendment in 1960, it did not include a GRAS exemption like it did for food additives just two year prior. *Compare* 21 U.S.C. § 321(t) (defining color additive), *with* 21 U.S.C. § 321(s) (defining food additive). Thus, the only way that any

potential color additive can be added to food is if there is a regulation that FDA affirmatively approves "prescribing the conditions under which such additive may be safely used[.]" 21 U.S.C. § 379e(a)(1)(A). There are no exceptions.

This statutory scheme reflected Congress's intent to be "particularly careful" with color additives. *Color Additives Amendment of 1960: Hearings on H.R. 7624 and S. 2197 Before the House Comm. on Interstate and Foreign Commerce*, 86th Cong., 2d Sess. at 108 (1960) (statement of Rep. James Delaney of New York). "[W]here Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." *Russello v. U.S.*, 464 U.S. 16, 23 (1983) (quoting *U.S. v. Wong Kim Bo*, 472 F.2d 720, 722 (5th Cir. 1972)). Unlike food additives, some of which "serve a useful purpose" and "have helped to develop and improve our food supply in many ways," color additives have "no nutrient value." *Color Additives Amendment of 1960: Hearings on H.R. 7624 and S. 2197 Before the H. Comm. on Interstate and Foreign Commerce*, 86th Cong., 2d Sess. 108 (1960) (statement of Rep. James

Delaney of New York). In fact, color additives "have no value at all, except so-called eye appeal." *Id*.

B. FDA's *color* additive regulations further this legislative intent, requiring "convincing evidence" to support a finding of safety: words that do not appear in the agency's *food* additive regulations.

Recognizing that Congress intended to be "particularly careful" with color additives, FDA promulgated regulations incorporating that heightened legislative concern. For example, FDA's food additive regulations define "safe" to mean there is "*reasonable certainty* in the minds of competent scientists that the substance is not harmful under the conditions of its intended use." 21 C.F.R. § 170.3(i) (emphasis added). In sharp contrast, as explained above, FDA defines "safe" in the color additive context to mean there is "*convincing evidence* that establishes with reasonable certainty that no harm will result from the intended use of the color additive." 21 C.F.R. § 70.3(i) (emphasis added). The standard of safety for color additives, therefore, requires "convincing evidence": words that are crucially absent from the standard for food additives. Thus, contrary to FDA's conclusion, the standard of safety for the two programs are *not* "the same" but, rather, distinct, just like the programs.

By their plain language and ordinary meaning the standards are different. "Convincing" means "[c]ausing one to believe that something is true or right; persuasive."[17] On the other hand, "reasonable" is by its long-established terms known to be a lesser legal standard, only requiring a showing that the interpretation is "[a]ccording to reason" as in "your argument is reasonable *but not convincing*."[18] Case law in other contexts further supports these distinctions. For example, in fraud cases, courts have found that "clear and convincing evidence" "requires more than [reasonable certainty]." *Candela v. U.S.*, 635 F.2d 1272, 1274 (7th Cir. 1980).

Multiple canons of construction support that these terms be given different meaning. For example, the whole-text canon, "calls on the judicial interpreter to consider the entire text, in view of its structure and of the physical and logical relation of its many parts." Antonin Scalia & Bryan A. Garner, *Reading Law: The Interpretation of Legal Texts* 167 (2012) (hereafter Scalia & Garner). The interpretive-direction canon provides that "[d]efinition sections and interpretation clauses are

[17] *Convincing*, Black's Law Dictionary (11th ed. 2019).

[18] *Reasonable*, Black's Law Dictionary (11th ed. 2019) (emphasis added).

to be carefully followed." Scalia & Garner, at 225. The surplusage canon holds that "it is no more the court's function to revise by subtraction than by addition." *Id.* at 174. Each of these canons require finding that FDA cannot read "convincing evidence" out of its regulation. And while these and other canons are ordinarily applied in statutory construction, this Court has applied canons of construction to regulations. *See Karczewski v. DCH Mission Valley LLC*, 862 F.3d 1006, 1015-16 (9th Cir. 2017); *Rainsong Co. v. FERC*, 151 F.3d 1231, 1234 (9th Cir. 1998).

Regarding the whole-text canon, the structure and physical relation of the Food Additives Amendment and Color Additives Amendment indicate that Congress intended that food additives and color additives be separately regulated. *See* 21 U.S.C. § 348 (food additives) *and* 21 U.S.C. § 379e (color additives). Moreover, by not including a GRAS exemption for color additives, Congress in unmistakable fashion showed its intent that color additives receive greater scrutiny than food additives. *Compare* 21 U.S.C. § 321(t) (defining color additive), *with* 21 U.S.C. § 321(s) (defining food additive). In other words, unlike potential food additives, the *only* way a potential color additive can be added to food is with FDA's affirmative approval.

In light of this structure and the physical and logical relation of the two statutes, the whole-text canon supports finding that Congress intended color additives to receive greater scrutiny than food additives. *Los Angeles Lakers, Inc. v. Fed. Ins. Co.*, 869 F.3d 795, 802 n.2 (9th Cir. 2017); Scalia & Garner, at 167.

In furtherance of these statutory distinctions, FDA promulgated distinct regulatory definitions of "safe" for food and color additives. Under the interpretive-direction canon, a careful reading of the two definitions reveals that one definition contains language that the other does not. *Id*. at 225. FDA could have drafted the color additive standard of safety to be identical to the food additive standard of safety, but it did not. Rather, FDA required there be "convincing evidence" to support the safety of color additives, words that are conspicuously absent from the food additive standard of safety.

FDA's construction also impermissibly renders the "convincing evidence" provision surplusage. *Id.* at 174. In construing administrative regulations, "it is presumed that *every phrase* serves a legitimate purpose and, therefore, constructions which render regulatory provisions superfluous are to be avoided." *Rainsong Co.* 151 F.3d at

1234 (quoting *Hart v. McLucas*, 535 F.2d 516, 519 (9th Cir. 1976)) (emphasis added). By equating the color additive and food additive standards of safety, FDA renders the "convincing evidence" provision of the color additive standard surplusage. Scalia & Garner, at 174.

Given that these standards are distinct, and should be applied as such, FDA cannot ignore those differences. This Court has made abundantly clear that a regulatory agency does not get to ignore its own standard of safety. *See Nat. Res. Def. Council*, 735 F.3d at 884 ("EPA may wish to revisit its standards in the future, but it cannot ignore them."); *Nw. Coal. for Alts. to Pesticides (NCAP) v. U.S. E.P.A.*, 544 F.3d 1043, 1052-53 (9th Cir. 2008) (remand where EPA failed to explain its departure from established safety factor). Yet by asserting that the standard of safety for color additives is "the same" as the standard of safety for food additives, FDA did just that, reading "convincing evidence" out of the standard of safety for color additives.

The decision's unambiguous language shows that FDA applied the wrong legal standard. *See* ER004 ("although the regulatory programs are distinct, *the standard of safety*—a reasonable certainty of no harm from the intended use—*is the same* for food additives, color additives,

and GRAS substances"); ER004. ("[t]he totality of evidence presented in the *color* additive petition indicated that there is a *reasonable certainty* that soy leghemoglobin protein and *P. pastoris* yeast proteins do not pose any unique allergenicity risks when consumed"); ER006 ("[u]nder § 70.3(i), a *color additive* is safe if there is a *reasonable certainty* in the minds of competent scientists that the substance is not harmful under the intended conditions of use") (emphases added).[19] This error rendered its decision contrary to law, requiring vacatur of the approval. FDA "may wish to revisit its standards in the future, but it cannot ignore them." *Nat. Res. Def. Council*, 735 F.3d at 884.

C. Color additives and GRAS substances also do not have the same standard of safety.

FDA's attempt to equate color additives with GRAS substances is even more egregious than its attempt to improperly apply the food additive provision. That is because GRAS substances are exempted from the FFDCA's definition of "food additive" and, therefore, do *not*

[19] The last quotation is especially glaring as it quotes verbatim the food additive standard of safety while purporting to quote the color additive standard of safety. *Compare* 21 C.F.R. § 170.3(i), *with* 21 C.F.R. § 70.3(i).

undergo FDA premarket review and approval. *See* 21 U.S.C. §§ 321(s), 348. As stated, and critically, "[t]here is no [GRAS] exemption to the definition of a color additive."[20]

And while the recently finalized GRAS rule purports to "require the same quantity and quality of scientific evidence" for GRAS substances "as is required to obtain approval of a food additive," 21 C.F.R. § 170.30(b), as explained above, under the rule FDA makes no determination of safety at all for GRAS substances; they are self-certified. Moreover CFS and other public interest organizations are currently challenging that rule as unlawful for, *inter alia*, failure to achieve the stated intent of the regulation. *See Ctr. for Food Safety v. Price*, No. 17-CV-3833 (VSB), 2018 WL 4356730 (S.D.N.Y. Sept. 12, 2018), ECF No. 44 (order denying motion to dismiss as to CFS and another public interest consumer group).

Even assuming *arguendo* that the GRAS rule does require the same quantity and quality of scientific evidence for GRAS substances as is required for *food* additives, that is irrelevant for the color additive at

[20] FDA, *Color Additives History*, https://www.fda.gov/industry/color-additives/color-additives-history (last visited Aug. 17, 2020).

issue here. Color additives, as explained *supra*, require *convincing evidence* of their safety.

D. At the very least, FDA's decision is hopelessly vague, making it impossible to determine what standard of safety it applied.

At a minimum, FDA's repeated conflation of the standards of safety for color additives, food additives, and GRAS substances renders its decision unlawfully "vague, making it impossible . . . to determine" what standard of safety FDA used in reviewing Impossible Foods' petition. *See NCAP*, 544 F.3d at 1051. In that case, Congress directed EPA to set an additional tenfold margin of safety for infants and children when determining tolerance levels for pesticide residues in food. EPA could deviate from tenfold margin of safety but only if had "reliable data" to support the deviation. The court said that "EPA's Final Order is vague, making it impossible for us to determine whether the EPA's deviations from the 10x child safety factor . . . were in fact supported by reliable data[.]" *NCAP*, 544 F.3d at 1051.

By treating all three standards of safety "the same," FDA conflated the standards of safety for food additives and GRAS substances with color additives. In other words, at a minimum, FDA's

decision is "vague, making it impossible . . . to determine" what standard of safety it used in reviewing Impossible Foods' color additive petition. *Id.* This vagueness abounds in FDA's denial of CFS's objections.

For example, CFS explained that FDA's excessive reliance on the information Impossible Foods submitted in support of its GRAS notice—where it sought to *avoid regulation* of soy leghemoglobin as a food additive—was improper for purposes of reviewing the company's color additive petition. ER014-16. In response, FDA "acknowledge[d] that the safety studies conducted in support of [Impossible Foods'] GRAS notice 737 were submitted in support of" the company's color additive petition. ER004. Despite this, FDA claims that it nevertheless "specifically evaluated" soy leghemoglobin's safety *as a color additive*. ER004.

However, in the very next sentence, FDA contends that the standards of safety for color additives, food additives, and GRAS substances are "the same." ER004. But FDA could not have "specifically evaluated" soy leghemoglobin's safety as a color additive if it considers the standard of safety for color additives, which requires *convincing evidence*, "the same" as that of food additives and GRAS substances,

which do not. Thus, at a minimum, FDA's denial of CFS's objections is "vague, making it impossible . . . to determine" what standard of safety FDA used. *NCAP*, 544 F.3d at 1051.

II. FDA FAILED TO SUPPORT ITS DECISION WITH SUBSTANTIAL EVIDENCE.

In addition to applying the wrong legal standard of safety for color additives, FDA's decision also lacks substantial evidence. In order to study and predict potential chronic effects in humans, the toxicity study guidelines at issue direct color additive petitioners to conduct a subchronic toxicity study, or rodent-feeding trial, on a *minimum* of 20 animals per sex per dosage group for a *minimum* of 90 days. ER267-77 (emphases added), as well as a chronic toxicity study, or rodent-feeding study for a minimum of 12 months (one year). ER288. Impossible Foods did not meet even these minimum requirements.

Instead, Impossible Foods conducted only a *28-day* rat-feeding study with only *ten* animals per sex per dosage group. ER311-312. But even in that limited, inadequate study, statistically significant toxicological effects were nevertheless observed in some rats fed soy leghemoglobin that could indicate health concerns related to tissue damage, kidney disease, inflammation, and cancer. ER314-319, 091-92,

005. The fact that this study did not comply with FDA's *minimum* guidelines for both study duration and number of test animals and still resulted in statistically significant toxicological effects should have prompted longer-term studies that complied with FDA guidelines.

But FDA discounted these observed toxicological effects because they "did not occur in both sexes," a rationale that appears nowhere in the agency's guidelines for subchronic toxicity studies. ER005, ER267-277. Nor did FDA supply any rationale to support with substantial evidence its conclusion that they can interpret (and discount the effects) of this study given its limited test size and length. For each of these reasons, FDA's decision is not supported by substantial evidence and must be vacated.

A. Impossible Foods' 28-day rat-feeding study with only ten animals per sex per dosage group did not meet FDA's *minimum* requirements for subchronic toxicity studies.

As explained above, FDA's Redbook directs food manufacturers in determining the need for and design of various studies to test the safety

of food ingredients[21] added to food. ER151. This guidance "specifically describe[s] the type of data that [FDA] *expect[s]* petitioners to generate or rely upon for safety decisions on food ingredients," including color additives. ER004 (emphasis added). Chapter IV.C. of the Redbook details how petitioners like Impossible Foods should design and conduct "specific toxicity studies" for food ingredients. ER147-149.

One of these specific studies, Subchronic Toxicity Studies with Rodents, is in Chapter IV.C.4.a. ER267. Here, FDA instructs food manufacturers on, *inter alia*, the minimum duration and the minimum number and sex of test animals required for such studies. For duration, "[a]nimals should be exposed to the test substance 7 days per week for a *minimum* of 90 consecutive days (3 months)" but perhaps "up to 12 months" if needed. ER267, 280 (emphasis added). Regarding the number of test animals, FDA directs "experimental and control groups should have *at least* 20 rodents per sex per group." ER268 (emphasis added). According to FDA, this minimum number of rodents per sex per

[21] The Redbook defines "food ingredients" to include "food additives and color additives used in food" as well as "food contact substances" and "substances which are classified as [GRAS]." ER151.

group is critical "to permit a meaningful evaluation of toxicological effects." ER268.

Results from these *subchronic* toxicity studies are used to help design future *chronic* (i.e., long-term) studies of the test substance. ER267. For example, if a subchronic toxicity study indicates potential kidney damage from a test substance at a certain dosage, that could help design a future chronic toxicity study focused on the kidney at the same or higher dose levels. It is essential then that subchronic toxicity studies are designed according to the minimum requirements discussed above to ascertain whether longer-term studies are needed. ER267.

In support of its color additive petition, Impossible Foods claims that it conducted a rat-feeding study "designed to meet the guidelines" in Redbook Chapter IV.C.4.a. (Subchronic Toxicity Studies with Rodents). ER311. FDA agreed that this study was purportedly "conducted following [its] . . . guidelines." ER323. However the record shows this was *not* the case and that Impossible Foods strayed far from the minimum requirements in Redbook Chapter IV.C.4.a. for both duration and the number of animals per sex per group. Despite these statistical weaknesses, statistically significant toxicological effects were

still observed in some of the rats fed soy leghemoglobin, which should have prompted additional subchronic and chronic toxicity testing. FDA did not require, and Impossible Foods did not do, any additional subchronic or chronic studies.

First, it is undisputed that Impossible Foods' rat-feeding study was not conducted in support of its *color additive* petition. Rather, the company resubmitted a previous study conducted in support of its earlier *GRAS* notice for soy leghemoglobin. ER004 (FDA acknowledging that "the safety studies conducted in support of GRAS notice 737 were submitted in support of" Impossible Foods' color additive petition). As explained above, GRAS substances are an exemption from the definition of food additive, for which there is no higher "convincing evidence" requirement. Whatever studies Impossible Foods conducted in support of its earlier GRAS notice (*i.e.*, to *avoid* regulation of soy leghemoglobin as a food additive) in no way indicates that those studies satisfy the higher convincing evidence standard for color additives.

Second, regardless of the original purpose of its rat-feeding study, Impossible Foods' claim that it complied with Chapter IV.C.4.a. of the Redbook is wrong. ER311. As explained above, this chapter outlines the

process for conducting subchronic toxicity studies in rodents. *See* ER267-277. Key here are two experimental design requirements: testing duration and number of test animals. The guidance specifies that for studies submitted in support of a color additive petition, "[a]nimals should be exposed to the test substance 7 days a week for a *minimum of 90 consecutive days*." ER270 (emphasis added). The guidance also says that "experimental and control groups should have at least 20 rodents per sex per group." ER268.

Rather than conducting a new study that satisfied these requirements, Impossible Foods chose to just resubmit the study conducted in support of its earlier GRAS notice, which included just *ten* rodents per sex per group and was conducted over a period of just *28 days*. ER311-312, ER289; ER004. This is well short of the minimum requirements for duration and number of test animals for subchronic toxicity studies. In other words, Impossible Foods did not comply with the "specifically describe[d] . . . type of data that [FDA] expect[s] petitioners to generate or rely upon for safety decisions" related to color additive petitions. ER004.

These failings matter. Again, at issue here is the human safety to eat soy leghemoglobin, a novel color additive for which "there is no history or knowledge of human dietary exposure." ER081. On the other side of the regulatory coin, Impossible Foods self-certified that soy leghemoglobin is GRAS, with no FDA approval of safety. So the color additive review is the *only meaningful* FDA review of this never-before-eaten GE substance.

This makes the rat-feeding study one of *the* critical components to judge if this GE substance is safe to eat: for children and adults. But Impossible Foods (and FDA) cut corners: the rat-feeding study is *less than 1/3* of the number of days required (28 instead of 90), and included just 50% of the test animals (10 rats per sex per group instead of 20). And these are just FDA's *minimum* requirements for duration and number of animals for subchronic toxicity studies.

There is a reason that there are minimum standards for scientific rigor in studies. Indeed, FDA explains in the subchronic toxicity guidelines at issue here that, for example, the minimum number of test animals per sex helps ensure "a meaningful evaluation of toxicological effects." ER268. FDA cannot avoid its own regulations or guidelines it

sets itself. *See Pollinator Stewardship Council,* 806 F.3d at 531-32; *Nat. Res. Def. Council*, 735 F.3d at 883-84; *NCAP*, 544 F.3d at 1052-53.

By relying on Impossible Foods' 28-day study, with just half the rodents called for in its guidance, FDA cannot ensure, with convincing evidence, that there was a "meaningful evaluation of toxicological effects." ER268. For the same reasons, FDA's decision lacked substantial evidence.

Third, despite falling well short of the subchronic toxicity guidelines, the 28-day study still resulted in statistically significant observed effects in test animals. ER314-319, ER091-92, ER005. Both this and the anticipated consumption levels should have prompted FDA to require more extensive toxicity studies, including a real subchronic (i.e., 90 days with at least 20 rats per sex per group) and chronic studies (minimum 1 year).

This is supported by FDA's Summary Table of Recommended Toxicological Testing for Additives in Food and is part of the Redbook. ER165.[22] This table defines three "concern levels" (I, II or III) based on

[22] This record cite contains an inactive hyperlink to the Summary Table, which is accessible at: https://www.fda.gov/regulatory-

human exposure to a compound and its toxicological potential, and recommends distinct batteries of toxicological tests for each concern level (CL). Even assuming soy leghemoglobin falls into the lowest (safest) of three toxicological potential categories (Structure Category A), daily human exposure to soy leghemoglobin far exceeds the level triggering the CL III battery of tests, which include both subchronic and chronic rodent studies, among others.[23]

Moreover, Impossible Foods' stated goals underscore the need for chronic testing. For example, the company says its "mission demands relentless growth every year," which means "making the Impossible Burger available to mainstream, mass-market consumers around the

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information/search-fda-guidance-documents/guidance-industry-summary-table-recommended-toxicological-testing-additives-used-food.

[23] The trigger for CL-III testing of Structure Category A compounds is daily human exposure > 1,000 ppb, which is equivalent to 50 micrograms (ug) per kilogram (kg) body weight (bw) per day, assuming a 3 kg daily diet (see note below the "Concern Levels" graphic). The estimated intake of soy leghemoglobin is 4.8 or 10.4 mg/kg bw/day (mean or 90th percentile, respectively) for the U.S. population 2+ years of age. ER296 (see Table 4). Converting from mg to ug (multiply by 1,000) gives a daily intake of soy leghemoglobin of 4,800 or 10,400 ug/kg bw/day, far exceeding the CL-III trigger of 50 ug/kg bw/day.

world."[24] The ultimate goal is to entirely "replace the use of animals as a food-production technology, globally, by 2035."[25] In order to achieve this, Impossible Foods "need[s] to scale up more than *100,000-fold*," meaning that "on average, [it] need[s] to double [its] production, sales and impact every year for the next 16 years."[26]

Already, Impossible Foods has introduced additional products containing the soy leghemoglobin color additive, including meatless pork and sausage products.[27] While CFS avidly supports plant-based eating, the rapid growth and marketing of these products means that more and more people are going to be exposed to a substance that, until very recently, was unknown to the human diet. And that exposure could be high for people who eat these products on a regular basis, which is what Impossible Foods wants. That is why FDA should have required

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[24] Impossible Foods, *Impact Report 2019*, https://impossiblefoods.com/mission/2019impact/.

[25] Impossible Foods, *If Not Now, Then When?*, https://impossiblefoods.com/mission/2019impact/letterfromtheceo/.

[26] Impossible Foods, *If Not Now, Then When?*, https://impossiblefoods.com/mission/2019impact/letterfromtheceo/ (emphasis added).

[27] *See* Impossible Foods, *Impossible Products*, https://impossiblefoods.com/food/.

subchronic and chronic toxicity studies before approving this color additive.

B. FDA relied on factors not supported by its guidance to dismiss statistically significant toxicological effects.

In addition to providing direction on how to design toxicity studies, FDA's guidance also directs food manufacturers to observe test animals throughout the duration of the study to look for various conditions and behaviors that could indicate a safety issue with the test substance. This includes, for subchronic toxicity studies, "[r]outine cage-side observations should be made on all animals at least once or twice a day throughout the study for general signs of pharmacologic and toxicologic effects, morbidity and mortality." ER272. The guidance further explains that an "expanded set of clinical evaluations, performed inside and outside the cage, should be carried out" in subchronic toxicity studies in rodents "to enable detection not only of general pharmacologic and toxicologic effects but also neurologic disorders, behavioral changes, autonomic dysfunctions, and other signs of nervous system toxicity." ER272.

In denying CFS's objections, FDA admits there were "statistically significant differences" observed in rats fed soy leghemoglobin when

compared to control animals during the 28-day feeding study. ER005. These statistically significant differences included: (1) unexplained transient decrease in body weight gain; (2) increase in food consumption without weight gain; (3) changes in blood chemistry; (4) decreased reticulocyte (immature red blood cell) count (which can indicate anemia and/or damage to bone marrow where red blood cells are produced); (5) decreased blood clotting ability; (6) decreased blood levels of alkaline phosphatase (which can indicate malnutrition and/or celiac disease); (7) increased blood albumin (which can indicate acute infection or damage to tissues) and potassium values (which can indicate kidney disease); (8) decreased blood glucose (low blood sugar) and chloride (which can indicate kidney problems); and (9) increased blood globulin values (which are common in inflammatory disease and cancer). ER092.

Reviewing the results of this feeding study, two researchers explained, "[t]he fact that these changes were seen in spite of the statistical weaknesses of [Impossible Foods' 28-day] study *gives particular reason for concern*." ER092 (emphasis added). They further cautioned that:

> . . . the fact that there were so many statistically significant changes in multiple organs and systems suggests that closer

> *scrutiny of the safety of [soy leghemoglobin] is urgently required*. The apparent randomness of the effects may be due to the fact that the study design was *statistically weak*. And it is well known that toxic effects do not always follow a linear dose response pattern. Dismissing the findings as irrelevant appears irresponsible.

ER093 (emphases added). But that is precisely what FDA did.

To do so, FDA stated that because the "statistically significant differences" observed in Impossible Foods' 28-day study "did not occur in both sexes," they "were incidental and not treatment-related." ER005. However, there is no basis whatsoever in FDA's subchronic toxicity study guidelines requiring statistically significant differences to "occur in both sexes" in order to consider those difference treatment-related. ER267-77. More fundamentally, FDA cannot determine statistically significant effects are merely "incidental" based upon such a small sample size. The subchronic toxicity study guidelines require a minimum of *20 rats* per sex per group "to permit a *meaningful* evaluation of toxicological effects." ER268 (emphasis added). Impossible Foods' too-short 28-day study only consisted of *10 rats* per sex per group. ER311-312. This could not provide a "meaningful evaluation of toxicological effects." ER268.

For these reasons, FDA's decision is not supported by substantial evidence.

III. THE COURT SHOULD VACATE FDA'S DECISION

Because of FDA's violations of the FFDCA, the Court should set aside FDA's approval. *All. for the Wild Rockies v. U.S. Forest Serv.,* 907 F.3d 1105, 1121-22 (9th Cir. 2018) ("presumption of vacatur," unless defendants meet their burden to show otherwise); *Pollinator Stewardship*, 806 F.3d at 532 (remand without vacatur permitted only in "limited circumstances"); *Humane Soc. of U.S. v. Locke*, 626 F.3d 1040, 1053 n.7 (9th Cir. 2010) ("rare circumstances"); *Idaho Farm Bureau Fed'n v. Babbitt*, 58 F.3d 1392, 1405 (9th Cir. 1995) ("Ordinarily" vacatur applies unless "equity demands" otherwise).

In the Ninth Circuit, when determining whether to leave an agency action in place on remand, the court "weigh[s] the seriousness of the agency's errors against the disruptive consequences of an interim change that may itself be changed." *Nat'l Family Farm Coal.*, 960 F.3d at 1144 (quoting *Pollinator Stewardship*, 806 F.3d at 532). Here, the seriousness of FDA's errors are substantial and thus outweigh any potential disruptive consequences resulting from vacatur.

At issue is the safety of a substance added to food for which, as FDA unambiguously stated, "there is no history or knowledge of human dietary exposure." ER081. As such, FDA should have required *rigorous* studies that adhered to its toxicity guidelines for color additives in order to show, with convincing evidence, that soy leghemoglobin is safe to eat. At every opportunity, however, FDA took shortcuts in its approval of soy leghemoglobin as a color additive. First, FDA read "convincing evidence" out of its regulatory standard of safety for color additives. Second, FDA relied on a safety study that failed to comply with the minimum specific guidelines for subchronic toxicity studies. These "multiple errors" in approving soy leghemoglobin as a color additive resulted in understated risks as to the safety of this new color additive. *Nat'l Family Farm Coal.*, 960 F.3d at 1144.

The seriousness of these errors outweighs any potential disruptive consequences of vacatur. This Court has said in environmental cases, the inquiry focuses on the potential for harm *to the environment* from vacatur, not purely economic considerations, taking the purpose of the statute into account. *See, e.g.*, *Pollinator Stewardship*, 806 F.3d at 532; *see also Alliance for the Wild Rockies*, 907 F.3d at 1122; *Ctr. for Food*

Safety v. Vilsack, 734 F. Supp. 2d 948, 953 (N.D. Cal. 2010) ("In light of the limited circumstances in which the Ninth Circuit has determined that equity warranted remanding without a vacatur, it is not clear that economic consequences is a factor the Court may consider in environmental cases."). Here, the purpose of the statute is to protect public health from unsafe color additives. From a public health perspective, leaving FDA's decision in place risks more potential harm than vacating it. Once FDA obtains adequate long-term studies, it may conclude that a lower amount of the color additive is required to ensure with convincing evidence that soy leghemoglobin is in fact safe. *Pollinator Stewardship*, 806 F.3d 532.

CONCLUSION

Impossible Foods filed a color additive petition for soy leghemoglobin, a novel GE substance for which "there is no history or knowledge of human dietary exposure." In support of that petition, Impossible Foods submitted a study to establish the safety of soy leghemoglobin but that study did not comply with the minimum FDA requirements for either duration or number of test animals per sex per group in such a study. And despite the statistical weaknesses of this

study, it still turned up potential health-related effects in some rats that should have prompted additional, longer-term studies.

But FDA did not require that. Instead, FDA lowered the bar even further for Impossible Foods by reading "convincing evidence" out of the color additive regulations. This all but ensured that soy leghemoglobin would receive no greater scrutiny as a color additive than when Impossible Foods self-determined it was GRAS. FDA was not "particularly careful" with this color additive that is now in products on grocery store shelves across the country.

For the reasons stated above, Petitioner requests the Court vacates FDA's decision, and remands for further proceedings consistent with this Court's decision.

Respectfully submitted this 18th day of August, 2020.

/s/ Ryan D. Talbott

Ryan D. Talbott
Sylvia Shih-Yau Wu
2009 NE Alberta St., Suite 207
Portland, OR 97211
T: (971) 271-7372
rtalbott@centerforfoodsafety.org
swu@centerforfoodsafety.org

Counsel for Petitioner