No. 20-70747

IN THE

United States Court of Appeals for the Ninth Circuit

CENTER FOR FOOD SAFETY,

Petitioner,

v.

U.S. FOOD & DRUG ADMINISTRATION; STEPHEN M. HAHN, in his official capacity as Commissioner,

Respondents,

IMPOSSIBLE FOODS INC.,

Intervenor.

On Petition for Review from the
United States Food and Drug Administration
Docket No. FDA-2018-C-4464

BRIEF FOR INTERVENOR IMPOSSIBLE FOODS INC.

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RULE 26.1 CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1, Intervenor Impossible Foods Inc. states that it has no parent corporation and no publicly traded corporation holds more than ten percent of its stock.

/s/ Catherine E. Stetson
Catherine E. Stetson

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INTRODUCTION

Impossible Foods Inc. ("Impossible") recognizes that animal agriculture poses a significant threat to our environment. Its mission is to develop plant-based meats that will reduce demand for animal protein. In support of that mission, Impossible is developing plant-based products that match or exceed their animal counterparts in terms of taste, nutritional value, and overall culinary experience. After extensive study, Impossible had a breakthrough: A key component of what makes meat "meaty"—a chemical compound known as "heme"—can be extracted from the roots of soy plants, in the form of soy leghemoglobin. And, almost as important, soy leghemoglobin can be produced at a useful scale through fermentation of a genetically modified strain of yeast.

For over six years now, Impossible and the U.S. Food and Drug Administration (FDA) have repeatedly evaluated and confirmed the safety of soy leghemoglobin produced this way. Impossible has partnered with leading scientific experts to conduct studies from many different angles, examining any potential toxicity, allergenicity, and even genetic effects. FDA reviewed and vetted those studies, commissioning not one but two independent reports from its own scientists. And, after reviewing all this evidence, FDA concluded that there was "convincing evidence establishing with reasonable certainty that no harm will result from the intended use," ER144—applying the definition of safety it uses for

color additives, 21 C.F.R. § 70.3(i), as soy leghemoglobin imparts a reddish-brown color to uncooked products.

Petitioner the Center for Food Safety ("the Center") now asks this Court to step in and displace the agency's considered judgment. That request, however, is not grounded in any cognizable assertion of harm. Instead, the Center rests its petition on generalized "concerns" of four of its members, which are too vague and speculative to give this Court jurisdiction under Article III of the Constitution or the Food, Drug, and Cosmetic Act (FDCA).

On the merits, the Center's arguments are equally thin. Its first argument, that FDA employed the wrong standard of safety in the challenged action, rests on a clear misreading of the agency's orders. As for the substance of FDA's determination, the Center focuses on just one study out of all the evidence FDA considered, offering critiques of that study based on an online commentary article. Several of those critiques were not presented to the agency during the regulatory comment period below. And, regardless, this Court's precedents rightly forbid displacing an agency's expert determination based on such meager fare.

Along the way, the Center attempts to kick up dust by alluding to a variety of irrelevant issues. It is therefore worth listing all the things this case is *not* about: It is not about genetic engineering; the Center has abandoned on appeal its objection based on that process. It is not about whether other companies are likely

to voluntarily submit their ingredients to FDA for premarket review; Impossible did so, twice. And it is not about FDA's process for reviewing food additives[1]; this is a color additive listing.

Instead, this case is about whether the Center can invoke this Court's jurisdiction based on cursory allegations of "concern" and whether it can convince this Court to displace the FDA's expert scientific judgment. Because the Center plainly cannot do either, the petition should be dismissed, or else denied.

STATEMENT OF JURISDICTION

The Center invokes this Court's jurisdiction under 21 U.S.C. § 371(f)(1). That provision allows, "[i]n a case of actual controversy," a "person who will be adversely affected" by a color additive listing to "file a petition" for review. *Id.* The Center claims to satisfy this statutory requirement and Article III's standing requirement based on declarations filed by four of its members. Because those members' concerns are too generalized and speculative, however, this Court lacks jurisdiction under both Article III and Section 371(f)(1). *See infra* Part I.

STATEMENT OF THE ISSUES FOR REVIEW

1. Whether the Center has standing under Article III of the U.S. Constitution or 21 U.S.C. § 371(f)(1).

[1] The Center has filed a separate case about the food additive process. *See Ctr. for Food Safety v. Price*, No. 1:17-cv-03833-VSB (S.D.N.Y.).

2. Whether FDA applied the correct regulatory standard in evaluating Impossible's color additive petition.

3. Whether FDA supported its decision with substantial evidence.

STATEMENT OF THE CASE

A. Legal Framework

Through the FDCA, Congress has entrusted FDA with regulating two types of ingredients: food additives and color additives. 21 U.S.C. §§ 348, 379e. The statute defines "food additive" broadly to include, with certain exceptions, "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food." *Id.* § 321(s). Foods "generally recognized as safe"—GRAS—are exempt from the definition of "food additives." *See id.* In other words, if a substance is GRAS, it is not a food additive. *Id.*

Color additives are any "dye, pigment, or other substance . . . when added or applied to a food" that are "capable (alone or through reaction with other substance) of imparting color thereto," excluding any substance "the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring." *Id.* § 321(t)(1). "[C]olor additive[s]" are expressly excluded from the statutory definition of "food additive." *Id.* § 321(s)(3).

The Act charges FDA with maintaining lists of food and color additives that are "safe" for use. *Id.* § 379e(b); *see also id.* § 348(a)(2). For both food and color additives, Congress has directed FDA to implement by regulation a system for food producers to submit ingredients for listing as safe food or color additives. *See id.* §§ 348(b)(1), 379e(d)(1). By regulation, FDA has defined the word "safe" the same way in both contexts: "reasonable certainty that no harm will result from the [additive's] intended use." 21 C.F.R. § 70.3(i) (color additives); *see id.* § 170.3(i) (food additives) ("reasonable certainty . . . that the substance is not harmful under the conditions of its intended use").

With respect to the quantum of evidence necessary to make this finding, however, FDA employs different wording depending on whether the additive is a food additive or a color additive. For food additives, the evidence must be sufficient to establish safety "in the minds of competent scientists." *Id.* § 170.3(i). For color additives, there must be "convincing evidence" of safety. *Id.* § 70.3(i).

The FDCA does not require FDA to list or otherwise keep track of GRAS substances as it does for food and color additives. By regulation, however, FDA has implemented a system allowing interested parties to notify FDA that a substance is GRAS based on available scientific evidence. *See* Substances Generally Recognized as Safe, 81 Fed. Reg. 54,960 (Aug. 17, 2016). Companies regularly submit these notifications; FDA's public database lists over 900 such

notices. *See* 21 C.F.R. § 170.275. When FDA receives those notifications, it has three possible responses: (1) it may issue a "no questions" letter, indicating it has reviewed the data and has no questions about the GRAS conclusion; (2) it may inform the submitter that the notice failed to provide sufficient evidence to support a GRAS conclusion; or (3) if the submitter withdraws the notice, FDA may acknowledge that the GRAS notice has been withdrawn. *See* 81 Fed. Reg. at 55,015.[2]

FDA possesses substantial enforcement tools to ensure compliance with the FDCA's food and color additive provisions. Food that includes unsafe food or color additives is "adulterated," and therefore prohibited, under the Act. 21 U.S.C. §§ 331(a), 342(a)(2)(A), (c). FDA has the power to conduct investigations to determine whether any unsafe food or color additives are present. *See id.* § 372. If those investigations identify adulterated products, FDA has the power to enjoin further sale of those products, *id.* § 332, seize them, *id.* § 334, and impose criminal penalties, *id.* § 331. FDA also has at its disposal less formal tools, such as warning letters, to publicly notify a manufacturer that FDA has identified serious violations

[2] FDA began using this GRAS notification system over twenty years ago, although it was not formally adopted until 2016. The prior system, like this one, involved a purely "voluntary administrative procedure" that did not require food makers to notify FDA before using a GRAS substance. 81 Fed. Reg. at 54,965.

of the FDCA. *See* FDA, Regulatory Procedures Manual, ch. 4 (Mar. 2020).[3] The threat of these enforcement tools gives food manufacturers powerful incentives to obtain premarket review of new ingredients.

B. Impossible's Meat Products and Safety Testing

Animal agriculture is among the technologies most destructive to the global environment. Pat Brown, Impossible Foods, *The Mission that Motivates Us*, Medium (Jan. 23, 2018).[4] Formed in 2011, Impossible aims to reduce humans' adverse impact on the environment by working to replace animal-based food products like meat, fish, and milk with plant-based alternatives. *Id.* Impossible believes it can develop plant-based "meat that outperforms the best beef from a cow—not just in sustainability, cost and nutritional value, but in flavor, texture, craveability, and even 'meatiness.'" *Id.* The "magic ingredient" is heme, an iron-containing molecule that occurs naturally in every animal and plant cell: "You can't make meat without heme." *Id.* Key to Impossible's ground beef product is a particular, plant-based heme protein: soy leghemoglobin. *Id.*

1. "Soy leghemoglobin is derived from the root nodule of the soy plant." SER28. Soy has been safely consumed by humans for more than 5,000 years. *Id.*

[3] *Available at* https://www.fda.gov/media/71878/download.

[4] *Available at* https://medium.com/impossible-foods/the-mission-that-motivates-us-d4d7de61665.

Soy is the basis for many common food products, like tofu, soymilk, miso, and bean sprouts, and FDA has affirmed the safety of soy protein isolates in multiple products. *Id.* The U.S. Department of Agriculture has even allowed soy protein to completely replace animal protein in the National School Lunch Program. *Id.* And although there is no specific history of humans consuming soy root nodules in particular, related leghemoglobin proteins are found in soy stems, shoots, cotyledon, leaves, and root hair, which humans regularly consume. SER29.

Soy leghemoglobin occurs naturally, but to produce the protein at scale, Impossible uses a genetically modified strain of yeast, *Pichia pastoris* (*P. pastoris*), that expresses the protein when fermented. *See* SER11, SER15-23. *P. pastoris* belongs to a family of yeast that is widely used in food production and includes the yeasts traditionally used in Belgian beers. SER30. During the fermentation process, Impossible checks each batch for purity; any batch with microbial contamination affecting safety or quality is sterilized and discarded. SER16. At the end of fermentation, Impossible recovers the expressed soy leghemoglobin, removes impurities, and ensures that the resulting soy leghemoglobin concentrate conforms to company standards and is free of pathogens. SER15-16.

2. Before incorporating soy leghemoglobin into its products, Impossible thoroughly investigated whether it is safe for human consumption. *See* SER28-49.

Impossible compared the protein's structure to that of heme proteins humans already eat, as well as to known allergens and toxins. SER28-30. It evaluated soy leghemoglobin's toxicity. SER30-39. And it evaluated the protein's potential allergenicity. SER39-49. None of these studies raised a concern.

First, Impossible's evaluation of soy leghemoglobin's safety considered the protein's structure. SER28-30. Soy leghemoglobin's three-dimensional structure "is highly similar" to leghemoglobin proteins in corn, rice, and barley that humans regularly consume. SER29. Its structure and oxygen binding mechanism is also "similar to those of animal muscle . . . proteins." *Id.* And although its primary chemical sequence varies from the primary sequence of mammalian proteins, soy leghemoglobin is not significantly similar to any known allergens or toxins. *Id.* Moreover, the molecule released when soy leghemoglobin is cooked or digested in the stomach, known as heme B, is "functionally equivalent" to heme B molecules widely consumed by humans and other animals, meaning "there is overwhelming evidence that heme B-containing proteins . . . have been safely consumed throughout human history." SER29-30.

Second, going beyond the historical and structural evidence suggesting that soy leghemoglobin is safe for human consumption, Impossible commissioned several toxicity studies. SER31-39. Most relevant here, Impossible commissioned a 28-day dietary toxicology study in rats (the "Feeding Study"). SER32. The

Feeding Study was conducted by Product Safety Labs in accordance with FDA's good laboratory practices regulations. *Id.*

The Feeding Study involved "soy leghemoglobin preparation," or the final post-recovery product containing soy leghemoglobin, *P. pastoris* proteins, and stabilizer components. *See* SER15, SER32. The Study maintained four test groups of twenty rats, eighty in total. SER32-33. Each test group had 10 males and 10 females. *Id.* The first group was the control group; none of those rats received any soy leghemoglobin preparation. *Id.* The dosing among the other three groups was deliberately calculated to exceed likely human consumption: Those groups received the equivalent of 250, 500, and 750 mg per kg bodyweight per day of soy leghemoglobin, respectively. *Id.* "The highest dose was selected as it provides a safety factor of 100 times the consumption levels estimated in the 90th percentile estimated daily intake calculations." ER74. Experimenters observed many aspects of the physiological response, including ophthalmological reactions, body weights, blood chemistry, hematology, and urinalysis. SER33. They also conducted necropsies, upon completion of the study. *Id.*

None of the experimental observations revealed an adverse effect attributable to soy leghemoglobin preparation. *Id.* There were no mortalities, *id.*, or discernible effects on the eyes, SER96. The test groups' body weights (male and female) were comparable to the control group's. *Id.* And the few observed

differences were not observed in both sexes, were not dependent on the dose received, and were within expected biological variation. *See* SER97-98. Thus, they were not toxicologically significant. *Id.*[5]

Impossible also commissioned studies to evaluate the potential genotoxic activity of soy leghemoglobin preparation. SER37-39. A bacterial reverse mutation test evaluated the potential for gene mutations and found none. SER37-38. A chromosome aberration assay evaluated whether the preparation could induce structural chromosome aberrations in human lymphocytes, which it did not. SER37-39.

Third, because soy contains several allergenic proteins, Impossible investigated soy leghemoglobin's potential allergenicity. *See* SER40-47. Dr. Steve Taylor, a co-director of the Food Allergy Resource and Research Program (FARRP) at the University of Nebraska, concluded that "[s]oy leghemoglobin is very unlikely to pose any risk to soy-allergic consumers" because it is not derived from the seed (where known soy allergens are found) and bears no structural similarity to any known soy allergens. SER122. Impossible also enlisted Dr.

[5] Because the test and control animals used in the Feeding Study had distributions of estrous cycle stages that deviated from published reports, Impossible commissioned a follow-up study to ensure that only rats with regular cycles advanced to the dosing phase. SER33-36. That study demonstrated that even the highest dose of soy leghemoglobin preparation caused no effect in estrous cycles or reproductive organ pathology. SER35-36.

Richard Goodman from the University of Nebraska to assess the potential allergenicity and toxicity of soy leghemoglobin and the *P. pastoris* proteins present in the soy leghemoglobin preparation, consistent with the approach typically applied to novel proteins expressed in genetically engineered foods. SER41-47. Based on the weight of the evidence, Dr. Goodman concluded that neither soy leghemoglobin nor *P. pastoris* proteins raised health or safety concerns. SER47. Even so, Dr. Taylor recommended advising consumers that Impossible products contain proteins derived from soy to alert soy-allergic consumers. SER122-123. Impossible does so. *Id.*

In short, Impossible considered soy leghemoglobin's safety from all angles. Each study pointed to the same conclusion: The product is safe.

C. Procedural History

Impossible has been consistently transparent with FDA about its use of soy leghemoglobin derived from *P. pastoris*.

First, Impossible voluntarily notified FDA of its conclusion that soy leghemoglobin is GRAS and therefore does not require listing as a food additive. During that notification and review process, which lasted four years, FDA was anything but a rubber stamp. Impossible submitted its first GRAS letter to FDA in September 2014. FDA responded with some questions about Impossible's methods and evidence. *See* ER81-82. Impossible responded to those questions,

and ultimately conducted additional scientific analysis, including the Feeding Study, resubmitting its even-more extensive analysis to the agency in October 2017. *See* ER144. In July 2018, FDA issued a letter thoroughly reviewing Impossible's submission and "stating that [it] had no questions regarding its conclusion that soy leghemoglobin preparation is GRAS for its intended conditions of use." ER144; *see also* Letter from Dennis M. Keefe, Ph.D., Director, Office of Food Additive Safety and Center for Food Safety and Applied Nutrition, FDA, to Gary L. Yingling, Morgan, Lewis & Bockius LLP (July 23, 2018).[6]

Once the GRAS process was complete, Impossible voluntarily submitted a color additive petition as well, *see* SER1, ER143, to remove any doubt about the regulatory propriety of using soy leghemoglobin in food.[7] As the statute requires, 21 U.S.C. § 379e(d)(1), the agency published notice of Impossible's petition in the Federal Register. ER143.

On August 1, 2019, FDA issued its final rule approving Impossible's soy leghemoglobin preparation as a safe color additive in ground-beef analogue products—that is, products that are beefy, but not made from cow. ER143-145. The final rule considered whether there was "convincing evidence establishing

[6] *Available at* https://www.fda.gov/media/116243/download.

[7] The Center asserts that Impossible was *required* to submit soy leghemoglobin for approval as a color additive. Center Br. 25. Because Impossible voluntarily submitted its petition, this Court need not address whether it was required to do so.

with reasonable certainty that no harm will result from the intended use of the color additive." ER144 (citing 21 C.F.R. § 70.3(i)). After considering all the evidence, including the preparation's "manufacturing and stability," "projected human dietary exposure," "any impurities," and "toxicological data," FDA determined that Impossible's soy leghemoglobin preparation was "safe" for its intended use as a color additive. ER144-145.

The Center submitted six independent objections to the final rule. Only two issues, derived from a single objection,[8] have been presented for review: First, the Center contended that FDA incorrectly applied the food additive definition of "safety," rather than the color additive definition. *See* ER4. Second, the Center argued that FDA should not have accepted a 28-day feeding study as opposed to a 90-day feeding study that Impossible had originally considered performing, and that FDA overlooked supposedly "statistically significant differences" in blood chemistry and function observed in the Feeding Study. ER16, ER5.[9]

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[8] The Center stated this objection as follows: "FDA's reliance on Impossible Foods' GRAS Notice 737 violates the definition of 'safe' in 21 C.F.R. § 70.3(i)." ER14. Consistent with that framing, the Center's objection focused primarily on the *source* of evidence FDA used, not its substance. ER14-16. The two issues that are the subject of this appeal are buried in two paragraphs at the end of this discussion. ER16.

[9] The Center has abandoned five other objections: (1) its contention that FDA erred by approving soy leghemoglobin for all gound-beef analogue products; (2) its contention that FDA should require, as a condition of listing, that Impossible label its products as being soy- or yeast-based; (3) its contention that FDA should have

FDA rejected both of the Center's objections. With respect to the definition of "safe," FDA pointed out that it had "specifically evaluated" soy leghemoglobin's "safety as a color additive," using the definition from the part of the Code of Federal Regulations entitled "Color Additives," 21 C.F.R. § 70.3(i), which "defines 'safe' to mean there is convincing evidence that establishes with reasonabl[e] certainty that no harm will result from the intended use of the color additive." ER4. FDA also pointed out that the ultimate "standard of safety" for food additives and color additives is the same: "a reasonable certainty of no harm from the intended use." *Id.*

As for the Center's concerns about the Feeding Study, FDA disagreed that "a 90-day feeding study, rather than a 28-day feeding study" would be necessary. ER5. The agency pointed to evidence showing that the relevant proteins "were mostly digested in" 30 seconds "and could not be detected beyond 2 minutes under the conditions of the study." *Id.* Moreover, analysis showed that "the intact proteins" and "any fragments thereof are not likely to cause any adverse effects." *Id.* Thus, a 90-day study would have "no added utility for demonstrating the safety

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further studied the uncooked product; (4) its contention that FDA should have required additional testing related to the genetically-engineered method of manufacturing the soy leghemoglobin preparation; and (5) its contention that FDA should prepare an environmental assessment or environmental impact statement under the National Environmental Policy Act. FDA correctly rejected each of these objections. ER3-6, ER13-19.

of this ingredient." *Id.* The allegedly "statistically significant" differences, the agency explained, bore no relationship to the dose received, did not occur in both sexes, and "were within historical ranges of control values" for rats "commonly used in toxicological studies." *Id.* Thus, they were "not likely to be of biological or toxicological significance." *Id.*

Having rejected the Center's objections, FDA added soy leghemoglobin to its list of safe color additives. *See* 21 C.F.R. § 73.520. That rule has been in effect since December 19, 2019. ER7.

The Center filed this petition for review. It asserts organizational standing based on the interests of four of its members, who express an interest in purchasing Impossible products but harbor generalized "concerns" that FDA did not adequately review soy leghemoglobin preparation before listing it as safe. *See* A72, A79, A84, A90.

SUMMARY OF ARGUMENT

I. This Court lacks jurisdiction over the Center's petition because it is grounded purely on generalized, speculative, and unsubstantiated concerns.

To establish associational standing under Article III of the Constitution, the Center must show that at least one of its members faces an injury-in-fact. Even when asserting a procedural defect in agency action, the Center must show a

reasonable probability of a concrete, particularized, and imminent injury. *San Luis & Delta-Mendota Water Auth. v. Haugrud*, 848 F.3d 1216, 1232 (9th Cir. 2017).

The Center falls well short of that mark. It cites four declarations from its members, each of whom expresses "concerns" about the safety of soy leghemoglobin. Only one of those four declarations makes any effort to link these concerns to particular health issues, and the Center identifies no clinical or scientific testing supporting the member's subjective belief that such a link may exist. This Court has held that such generalized and speculative concerns cannot supply the necessary injury-in-fact. *See Nuclear Info. & Res. Serv. v. Nuclear Regul. Comm'n*, 457 F.3d 941, 949, 950-954 (9th Cir. 2006).

Even if the Center has cleared Article III's floor, it falls short of the statutory jurisdictional requirement to maintain a petition. The relevant provision requires a petitioner to show not just a possibility of injury but that the petitioner "will be adversely affected." 21 U.S.C. § 371(f)(1). The members' perfunctory expressions of concern do not make such a showing.

II. In evaluating Impossible's color additive petition for soy leghemoglobin, FDA applied the correct regulatory definition of safety, asking whether there was "convincing evidence establishing with reasonable certainty that no harm will result from the intended use of the color additive." ER144 (citing 21 C.F.R.

§ 70.3(i)). At least three separate times, FDA confirmed it was using that definition. ER4, ER6, ER144.

The Center nevertheless maintains that FDA wrongly applied the definition applicable to *food* additives, which examines whether "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). That argument rests on a clear misreading of FDA's response to its objections. The ultimate standard of safety—"reasonable certainty of no harm from the intended use"—is the same for both food and color additives. ER4. The Center's argument conflates the standard of *safety*, which is the same for both types of additive, with the standard of *proof*, which varies slightly. FDA plainly applied the color-additive standard rather than the food-additive standard.

III. The Center's contentions that FDA's decision is not supported by substantial evidence are all meritless.

First, the Center argues that the design of the Feeding Study is inconsistent with FDA's Redbook, the agency's guidance document for toxicology studies. But the Center failed to present that concern to the agency; its objections below never once mentioned or cited the Redbook. The argument is also meritless. The Redbook clearly specifies that its recommendations are not binding and that

context may justify deviations, and FDA reasonably explained all relevant aspects of the Feeding Study's design.

Second, the Center argues that FDA improperly ruled out certain supposedly statistically significant physiological effects on rats in the Feeding Study. Again, however, the Center misreads FDA's reasoning. In fact, FDA considered these observations and found that they were consistent with historical control values and not related to the rats' consumption of soy leghemoglobin.

In any event, the Center's narrow attacks on a single Feeding Study fail to account for the wealth of additional evidence supporting FDA's decision. The Center does not challenge any of that evidence on appeal, and it is more than sufficient to support FDA's decision regardless of the Center's concerns about the Feeding Study.

IV. Should the Court conclude that FDA must further clarify its reasoning, it should remand without vacatur. The Center's highly technical objections can be easily cured and do not justify potentially disrupting the widespread sales of Impossible's products—particularly given the complete absence of any evidence of adverse effects on a single consumer.

STANDARD OF REVIEW

This Court considers its subject-matter jurisdiction, including a petitioner's standing, de novo. *See FMC Med. Plan v. Owens*, 122 F.3d 1258, 1260 (9th Cir.

1997). The Court has "an independent obligation to determine whether subject-matter jurisdiction exists." *Arbaugh v. Y&H Corp.*, 546 U.S. 500, 514 (2006).

On the merits, this Court reviews FDA's decision in a color-additive petition deferentially. The agency's factual findings, if supported by substantial evidence, are conclusive. 21 U.S.C. §§ 371(f)(3), 379e(d). The Court "must affirm the [agency's] finding where there is such relevant evidence as a reasonable mind might accept as adequate to support a conclusion even if it is possible to draw two inconsistent conclusions from the evidence." *NRDC v. EPA*, 735 F.3d 873, 877 (9th Cir. 2013) (internal quotation marks omitted). And where, as here, "the agency is making predictions, within its area of special expertise, at the frontiers of science[,] a reviewing court must generally be at its most deferential." *Id.* at 877 (ellipses and internal quotation marks omitted); *see also United States v. Alpine Land & Reservoir Co.*, 887 F.2d 207, 213 (9th Cir. 1989) ("Deference to an agency's technical expertise and experience is particularly warranted with respect to questions involving . . . scientific matters."). An agency "is not required to support its finding with anything approaching scientific certainty." *ASARCO, Inc. v. Occupational Safety & Health Admin.*, 746 F.2d 483, 490 (9th Cir. 1984) (ellipses and internal quotation marks omitted).

This Court also owes deference to the Agency's understanding of the statutes and regulations it implements. *See Chevron, U.S.A., Inc. v. NRDC*, 467

U.S. 837, 844 (1984); *Kisor v. Wilkie*, 139 S. Ct. 2400, 2408 (2019). Even when, as here, the government does not expressly invoke that deference, courts "often pay particular attention to an agency's views in light of the agency's expertise in a given area, its knowledge gained through practical experience, and its familiarity with the interpretive demands of administrative need." *County of Maui v. Hawaii Wildlife Fund*, 140 S. Ct. 1462, 1474 (2020).

The Center attempts to conflate the "arbitrary and capricious" standard applied by district courts under the Administrative Procedure Act with the substantial evidence standard required by the statute here. *Compare* 5 U.S.C. § 706(2)(A), *with* 21 U.S.C. § 371(f)(3). Those two standards are not necessarily the same, and the Center cites no case holding as much. *See* Center Br. 31. In this case, however, the Center's first argument asserts a legal error, and its second is a classic "substantial evidence" challenge to the agency's reading of the scientific record. Thus, the Court need not confront any potential differences between the two standards in this case, and may simply apply the statutory "substantial evidence" standard. 21 U.S.C. § 371(f)(3).

ARGUMENT

The Center's petition faces a threshold jurisdictional obstacle: It rests on nothing more than a few members' speculative, generalized concerns. This Court should therefore dismiss the petition without reaching the merits.

The petition is also meritless. Its argument concerning the legal standard that FDA employed rests on an obvious misreading of the orders under review. Furthermore, its substantial-evidence arguments, which are largely not preserved for appeal, are precisely the classic type of nitpicking and scientific second-guessing that this Court has long held insufficient to overturn an agency's considered scientific judgment within its area of expertise. Thus, if the Court does not dismiss the petition, it should be denied.

I. THIS COURT LACKS JURISDICTION BECAUSE THE CENTER HAS IDENTIFIED PURELY SPECULATIVE CONCERNS ABOUT THE AGENCY'S LISTING OF SOY LEGHEMOGLOBIN.

The party invoking federal jurisdiction bears the burden of establishing jurisdiction, including its standing to sue. *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 561 (1992). Here, because the Center's challenge to FDA's approval of soy leghemoglobin comes directly to this Court on a petition for review, "petitioner[] [has] the burden to demonstrate a 'substantial probability' of standing," *Northwest Requirements Utils. v. FERC*, 798 F.3d 796, 805 (9th Cir. 2015) (quoting *Sierra Club v. EPA*, 292 F.3d 895, 898-899 (D.C. Cir. 2002)), which is "the same [burden] as that of a plaintiff moving for summary judgment in the district court," *Sierra Club*, 292 F.3d at 899.

A prerequisite for organizational standing is for "at least one identified member" to have standing to sue in his or her own right. *Summers v. Earth Island*

Inst., 555 U.S. 488, 498 (2009).[10] That is, the Center must show that an identified member has "(1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the defendant, and (3) that is likely to be redressed by a favorable judicial decision." *Spokeo, Inc. v. Robins*, 136 S. Ct. 1540, 1547 (2016). Where, as here, a party alleges a procedural injury, to show a cognizable "injury in fact, [a plaintiff] must allege . . . that (1) the [agency] violated certain procedural rules; (2) these rules protect [a plaintiff's] concrete interests; and (3) it is reasonably probable that the challenged action will threaten their concrete interests." *San Luis & Delta-Mendota Water Auth.*, 848 F.3d at 1232 (quoting *Nuclear Info. & Res. Serv.*, 457 F.3d at 949).

The Center has attempted to satisfy its burden on jurisdiction by attaching declarations to its opening brief from four of its members. The members' chief complaint is a generalized dislike of genetically engineered food. *See* A71-72, A76-78, A82, A89-90. But the Center has not presented to this Court its objection relating to the process of genetic engineering that Impossible uses to produce its soy leghemoglobin preparation. *See* ER5 (FDA rejecting this objection, concluding "there is no scientific basis to conduct additional testing . . . simply because of the methods used to develop the strain").

[10] The Center does not claim any injury to its own interests. *See* Center Br. 2-4.

In any event, none of the members alleges a direct injury to their health or safety—for example, any adverse health effects from soy leghemoglobin. *See generally* A68-73 (Kaluza Decl.); A74-79 (Kelley Decl.); A80-84 (Maker Decl.); A85-91 (Thomas Decl.). Instead, each member cites an interest in purchasing Impossible products, along with a vague "concern" about whether Impossible Burgers are safe to eat. A72 (Kaluza Decl. ¶¶ 10-11) ("I am concerned about whether Impossible Burgers are safe to eat," and whether FDA's approval of soy leghemoglobin "could put consumers at risk"); A78-79 (Kelley Decl. ¶ 12) ("I am concerned about whether Impossible Burgers are safe to eat . . . ."); A82 (Maker Decl. ¶ 6) ("I am concerned about the safety of Impossible Burgers."); A90 (Thomas Decl. ¶ 11) ("I am concerned about whether Impossible Burgers are safe to eat . . . .").

"Concern" does not confer standing. *See Mayfield v. United States*, 599 F.3d 964, 970 (9th Cir. 2010) (explaining that neither "speculation [n]or 'subjective apprehension' about future harm support standing" (quoting *Friends of the Earth, Inc. v. Laidlaw Envtl. Servs. (TOC), Inc.*, 528 U.S. 167, 184 (2000))). Indeed, this Court has previously found that similar allegations of "concern" were insufficient to establish an injury in fact. In *Nuclear Information & Resource Service*, several organizations challenged a federal rule that revised regulations governing the transportation of radioactive material. 457 F.3d at 944. The

organizational plaintiffs submitted member declarations expressing "generalized concern" that the agency action "may expose [them], as well as other members of the public, to adverse health consequences." *Id.* at 954. This Court found those declarations insufficient to establish standing. *Id.* at 953-954. Instead, they "simply express[ed] undifferentiated 'concerns' . . . and speculate[d] that unregulated transportation of radioactive material in general—*not this regulation in particular*—may present unspecified threats to their health." *Id.*

The same is true here. The declarations from the Center's members make no effort to articulate a reasonable probability that FDA's approval of soy leghemoglobin increases the chances that the members will experience any adverse health effects. They allege only a subjective, unsubstantiated, and abstract "concern" that it might—and even then, only if they choose to purchase and consume Impossible products.

Such generalized (and avoidable) concerns are not enough. *Id.* The closest any declaration comes to linking the final rule with *any* particular health interest is Ms. Maker's assertion that test results from the Feeding Study showed increased globulin (blood-protein) values in some rats. *See* A83-84 (Maker Decl. ¶ 9). But even then, Ms. Maker asserts only that "increased globulin values . . . *may* indicate

inflammatory disease and cancer." *Id.* (emphasis added).[11] Where a party invokes only an increased risk of future harm, it must show a "substantial" increase in risk to satisfy Article III. *In re Zappos.com, Inc.*, 888 F.3d 1020, 1026 (9th Cir. 2018) (internal quotation marks omitted); *see also Food & Water Watch, Inc. v. Vilsack*, 808 F.3d 905, 914 (D.C. Cir. 2015) (requiring "*both* (i) a *substantially* increased risk of harm and (ii) and *substantial* probability of harm with that increase taken into account" (internal quotation marks omitted)). "[A] speculative multi-link chain of inferences," like the one advanced by the Center and its members, does not establish a reasonable probability of such a substantial increase. *Zappos.com*, 888 F.3d at 1026; *see also Food & Water Watch*, 808 F.3d at 915-917 (plaintiffs lacked standing to challenge approval of a method of inspecting poultry based on allegations that more adulterated products would result where plaintiffs failed to explain or persuasively support *why* that result was likely).

Nor can the Center fall back on some members' assertions that they will avoid eating Impossible products absent additional FDA review. Even if not eating Impossible products could somehow be considered a "harm," parties "cannot manufacture standing merely by inflicting harm on themselves based on their fears

[11] As discussed in more detail below, FDA considered this observed increase in blood-protein values, and explained that those effects were incidental and not related to soy leghemoglobin. *Infra* at pp. 39-42. Ms. Maker does not dispute—or address—FDA's explanation. *See generally* A80-84 (Maker Decl.).

of hypothetical future harm that is not certainly impending" because such injuries "are not fairly traceable" to the conduct creating that fear. *Clapper v. Amnesty Int'l USA*, 568 U.S. 398, 416 (2013); *see also Food & Water Watch*, 808 F.3d at 919 (rejecting plaintiffs' efforts to "repackage" speculative injury through "self-inflicted injuries" (internal quotation marks omitted)). Indeed, at least one member, Ms. Maker, plans to continue eating Impossible Burgers, indicating that even she does not perceive that there is *substantial* likelihood that FDA's approving soy leghemoglobin as a color additive threatens her health or safety. A84 (Maker Decl. ¶ 11).

Two of this Court's recent cases finding standing illustrate what is missing here. In *California v. Azar*, California challenged a federal rule allowing a religious exemption to the Affordable Care Act's mandate that employers provide contraceptive care. 911 F.3d 558, 566 (9th Cir. 2018). California used declarations from citizens to support its standing. *Id.* at 572-573. Those declarations established a simple, direct link between the agency action and California's concrete economic interests: Citizens explained that in the absence of coverage for contraceptive care under their employers' plans, they would replace their employer coverage with coverage from the state, requiring extra expenditures from California. *Id.* California also pointed to the federal agency's own regulatory impact analysis, which reaffirmed this link. *Id.*

And in *National Family Farm Coalition v. EPA*, 966 F.3d 893 (9th Cir. 2020), petitioners challenged the Environmental Protection Agency's decision to register a new pesticide. *Id.* at 904. Specifically, the petitioners complained that EPA had not addressed evidence that the pesticide would kill milkweed, a food source for monarch butterflies. *See id.* at 906, 909. The Court held that the petitioners had established a "credible threat" sufficient to establish an injury, given the existence of "record evidence" that the registered pesticide impacted milkweed. *Id.* at 909, 917 (internal quotation marks omitted).

Unlike the challengers in *California v. Azar* and *National Family Farm Coalition*, the Center here has produced no evidence supporting the multi-step chain of inferences it asks this Court to accept; indeed, the Center has not even clearly articulated its logic. The only evidence the Center can point to in this record is an online commentary on the very regulatory action under review. *See* ER91-92, ER95-96 n.4. The article asserts, without citation to any clinical or peer-reviewed literature, that some of the observed effects on rats in the Feeding Study are indicative of various maladies. *See id.* That is far too thin a reed upon which to rest a claim that the Center's members face a substantially increased risk of illness. *See Nuclear Info. & Res. Serv.*, 457 F.3d at 953-954.

Even if the Center's member declarations satisfied the floor set by Article III, they would not clear the more substantial standard Congress set in its

jurisdiction-creating statute, which requires a showing that a petitioner "*will be* adversely affected" by the Agency's order. 21 U.S.C. § 371(f)(1) (emphasis added). The members' highly attenuated and speculative concerns fall well short of that threshold. *Cf. U.S. Cane Sugar Refiners' Ass'n v. McNutt*, 138 F.2d 116, 120-121 (2d Cir. 1943) (finding no jurisdiction under Section 371 where petitioner asserted only "tenuous likelihood of injury," and noting that more expansive conception would create such "opportunity for maintaining petitions to review . . . so unlimited as to be a serious threat to the practical administration of the statute").

II. FDA APPLIED THE CORRECT STANDARD OF SAFETY.

On the merits, the Center's lead argument is that FDA applied the standard of safety applicable to food additives, rather than the standard for color additives. Center Br. 32. That argument conflates the standard of *safety*—which remains the same across both types—with the standard of *proof*—which differs. The FDA's orders clearly applied the proper regulatory standard of safety, using the proper regulatory standard of proof, for color additives.

The FDCA requires FDA to determine that color additives are "safe" before listing them. 21 U.S.C. § 379e(b)(1). The statute does not further define the word "safe." Exercising its regulatory authority under the FDCA, *id.* § 371(a), FDA has defined "safe" to mean that there is "reasonable certainty" that no harm will result from the "intended use." 21 C.F.R. § 70.3(i) (color additives); *id.* § 170.3(i) (food

additives). That standard of safety thus remains the same across color and food additives.

The wording used for the standard of *proof* of safety varies, as explained above (at 5, 29). In the context of color additives, the agency must conclude "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) (emphases added).

A reader needs no more context to see that FDA applied the correct standards in adopting the rule under review. The final rule recites the appropriate definition of "safe" for color additives, citing Section 70.3(i) expressly, ER144, and then determines that "soy leghemoglobin as a color additive in ground beef analogue products is safe," ER145. In its response to the Center's objections, FDA reaffirmed that it was applying Section 70.3(i)—requiring "*convincing evidence* that establishes with *reasonabl[e] certainty* that no harm will result from the intended use"—and its conclusion that soy leghemoglobin satisfies that definition. ER4 (emphases added).

The Center's contrary argument depends on quoting two aspects of FDA's response to its objections out of context. The first is a simple clerical error: In the final summary at the end of the response, FDA confirms *for a third time* that its applying Section 70.3(i). ER6. But the agency then recites the language of the

standard for food additives, which appears in Section 170.3(i): "reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use." ER6. Given that FDA repeatedly—including in that same sentence—confirmed it was using the "convincing evidence" standard in Section 70.3(i), ER4, ER6, ER144, there is no cause to attribute this to anything other than oversight.

Second, the Center challenges FDA's observation that "the standard of safety" for food and color additives is the same. ER4. But FDA is correct: Both definitions consider whether there is "a reasonable certainty" that no harm will result. *Compare* 21 C.F.R. § 70.3(1) (color additives), *with id.* § 170.3(i) (food additives). The only difference is the amount of evidence necessary to satisfy that standard. Color additives require "convincing evidence," *id.* § 70.3(i), while food additives require evidence sufficient to establish "reasonable certainty in the minds of competent scientists," *id.* § 170.3(i). It is unclear whether there is any practical difference between the two—consider, after all, whether a "competent scientist" would be persuaded by evidence that is less than "convincing." But because FDA used the "convincing evidence" threshold here, ER4, that question can await another day.[12]

[12] These two sentences—a clerical error and a correct statement of the law—likewise do not make FDA's reasoning "hopelessly vague." Center Br. 41.

For the same reason, the Center's extensive recitation of legislative history and statutory structure (at 32-38) is beside the point. No one disagrees that Sections 70.3(i) and 170.3(i) use slightly different formulations for the evidentiary burden required to show the necessary "reasonable certainty."[13] The only relevant dispute is whether FDA applied the standard set out in Section 70.3(i). Any fair reading of the agency's reasoning confirms that it did.

To the extent the Center suggests (at 40) that the Court can *infer*, contrary to the language the agency used, that FDA applied the wrong standard because it relied on certain evidence that Impossible submitted along with its GRAS notice, that argument fails as a matter of basic logic. Even granting the Center's premise that the color-additive standard is more stringent than the food-additive and GRAS standards, there is nothing inconsistent about the notion that the same evidence might satisfy *both* standards. FDA never suggests, for example, that it finds the evidence sufficient in the color additive context because it also had no questions about the GRAS notice. Rather, it newly considered the evidence, under the proper legal framework for color additive petitions, ER4, ER144, and concluded the evidence met that standard, ER6, ER145.

[13] Moreover, in construing the definition of a *regulatory* provision, evidence of *congressional* intent in a provision that does not contain the key language is of marginal relevance.

III. FDA SUPPORTED ITS DETERMINATION THAT SOY LEGHEMOGLOBIN IS SAFE WITH SUBSTANTIAL EVIDENCE.

The Center's second argument is that FDA's approval of soy leghemoglobin was not supported by substantial evidence because the toxicity study submitted by Impossible was inadequate. Center Br. 43-56. To the contrary, FDA properly relied on and evaluated Impossible's Feeding Study, and that Feeding Study was only one component of a multifaceted evaluation of soy leghemoglobin's safety.

This Court's review of the issue is limited. "Substantial evidence means more than a mere scintilla but less than a preponderance; it is such relevant evidence as a reasonable mind might accept as adequate to support a conclusion . . . even if it is possible to draw two inconsistent conclusions from the evidence." *NRDC v. EPA*, 857 F.3d 1030, 1036 (9th Cir. 2017) (internal quotation marks and citations omitted). And "[w]hen, as in this case, the agency 'is making predictions, within its area of special expertise, at the frontiers of science . . . a reviewing court must generally be at its most deferential.' " *Id.* (quoting *NRDC*, 735 F.3d at 877). The Court does not "act as a panel of scientists that instructs the [agency] . . . , chooses among scientific studies . . . and orders the agency to explain every possible scientific uncertainty." *Northern Plains Res. Council, Inc. v. Surface Transp. Bd.*, 668 F.3d 1067, 1075 (9th Cir. 2011) (internal quotation marks omitted).

To support its petition for approval of soy leghemoglobin as a color additive, Impossible submitted a detailed analysis of the product's safety. SER28-49. Impossible evaluated past human exposure to soy products; considered the safety of the host yeast used to synthesize soy leghemoglobin, *P. pastoris*; and commissioned studies to evaluate soy leghemoglobin's potential genotoxicity and allergenicity. *See* SER28-31, SER37-49. Impossible also submitted its findings from the Feeding Study in rats that assessed the product's potential toxicity to humans. SER31-37, SER72-101, SER103-121. The Feeding Study "showed no evidence of toxicity in rats at the maximum dose tested" and "no clinically significant differences between groups in clinical observations, body weights, hematological parameters, clotting potential, or clinical chemistry for both sexes." SER48. Two FDA scientists conducted their own further reviews of the available evidence. ER289, ER320. Based on all the evidence, FDA "concluded that the data presented by the petitioner demonstrate that soy leghemoglobin is safe for its intended use in ground beef analogue products." ER6.

The Center contends that one component of this evidence—the Feeding Study—is flawed. Its argument is two-fold.

First, the Center argues that because FDA's non-binding guidance document, the Redbook, recommends a different design for toxicity studies than what was used by Impossible, the agency could not rely on the results of the

Feeding Study. Center Br. 44-53. This argument was not presented to the agency, and therefore should not be considered. If the Court nevertheless were to take up the argument, it could make quick work of it: The Redbook's guidance is not binding, and FDA reasonably explained why it was appropriate to deviate from the default design in this case.

Second, the Center argues that FDA unreasonably dismissed allegedly significant effects observed during the Feeding Study. *Id.* at 53-56. This argument is classic scientific second-guessing, and should be rejected.

A. The Redbook Does Not Establish Legally Enforceable Responsibilities, And FDA Reasonably Explained Why The Feeding Study's Design Was Justified.

The heart of the Center's "substantial evidence" argument is that FDA could not rely on the Feeding Study because the study did not strictly adhere to study-design recommendations in the Redbook. That argument was not presented to the agency below, *see* ER14-16, and this Court therefore need not consider it. *See Koretoff v. Vilsack*, 707 F.3d 394, 398 (D.C. Cir. 2013) (per curiam) ("We require the argument [petitioner] advances here to be raised before the agency, not merely the same general legal issue." (alteration in original) (internal quotation marks omitted)); *see also California ex rel. Becerra v. Azar*, 950 F.3d 1067, 1092 n.23 (9th Cir. 2020) (favorably citing *Koretoff*). Below, the Center objected to the study design without any reference to the Redbook, instead complaining that Impossible

had impermissibly changed course. ER16. The article the Center relied on to support that contention—an online commentary—likewise did not mention the Redbook. *See* ER88-95. FDA properly rejected the argument the Center raised, ER5, and the Court need not consider its new one. *Koretoff*, 707 F.3d at 398.

In any event, however, the argument is meritless. This Court is at its most deferential in considering FDA's expert scientific judgment regarding the sufficiency of a study's design. *NRDC*, 857 F.3d at 1036. Here, FDA exercised its expert scientific judgment with diligence and explained itself thoroughly.

1. The Center maintains that the Redbook required Impossible to conduct a toxicity feeding study that lasted at least 90 days, and therefore, FDA could not rely on the shorter Feeding Study. Center Br. 44-53.

The Center misreads the Redbook. While it advises that rodent studies are *generally* 90 days, and that "[i]n general," such studies "should have at least 20 rodents per sex per group," ER171, the Redbook explicitly clarifies that "FDA's guidance for toxicity studies for food ingredients . . . presents recommendations—not hard and fast rules," ER153. Indeed, the Redbook states that its recommended 90-day regime may be altered where justified. ER270.

Here, FDA determined that the Feeding Study's deviation from the Redbook's recommended 90-day study was justified. *See* ER5. In response to the Center's suggestion that FDA was required to conduct an independent study of soy

leghemoglobin's safety, citing an online report that criticized the Feeding Study, *see* ER16 (citing ER88-97), FDA explained that a longer feeding study was unnecessary, ER5. "[T]he digestibility studies in simulated gastric fluid showed that the soy leghemoglobin protein and *P. pastoris* proteins were mostly digested in 0.5 minutes and could not be detected beyond 2 minutes under the conditions of the study." *Id.* And this rapid digestion meant that "these proteins would no longer be available intact following oral administration in either a 28-day or 90-day study." *Id.* FDA also reasoned that "sequence analysis of the soy leghemoglobin protein and *P. pastoris* proteins and their known functions suggest that the intact proteins or any fragments thereof are not likely to cause any adverse effects." *Id.* In plain English: Because the proteins are rapidly digested and are unlikely to cause adverse effects, there was no utility to a longer study. *Id.* The Center does not refute—or even acknowledge—FDA's reasoned explanation in response to its objection. *See* Center Br. 43-56.

2. The Center also raises concerns about the number of rats featured in the study. This argument, which the Center alluded to in just half a sentence below (and without mentioning the Redbook), ER16, is meritless. Again, the Redbook explicitly allows for variations in study size, including studies of only 10 rodents per sex per group. *See* ER268. And although the Redbook states that toxicity studies "*should* have at least 20 rodents per sex per group," *id.* (emphasis added), it

also explains that "[t]he use of the word should . . . means that something is suggested or recommended, but not required," ER153. Indeed, "FDA's guidance documents, including [the Redbook], do not establish legally enforceable responsibilities." *Id.* The Center has offered no basis for converting the Redbook's recommendations into requirements. *See Nat'l Family Farm Coal.*, 966 F.3d at 920 (allowing EPA to rely on studies that varied from nonbinding agency guidelines).

Where, as here, an agency's guidance document "does not bind the [agency] . . . , the relevant question is whether, quite apart from the [guidance document], the [agency] acted unreasonably." *Sitka Sound Seafoods, Inc. v. NLRB*, 206 F.3d 1175, 1182 (D.C. Cir. 2000). FDA did not act unreasonably. The Redbook's recommendations on the number and sex of test rodents are designed only to "help ensure that the number of animals that survive until the end of the study will be sufficient to permit a meaningful evaluation of toxicological effects." ER268. And the Redbook repeatedly suggests that the sufficient number for this "meaningful evaluation" generally is ten rodents, exactly the number evaluated in the Feeding Study.[14] *See* ER272 (suggesting that blood samples be taken from "10 rodents of each sex per group at least three times during the study" for hematology profile clinical testing); ER273 (suggesting clinical chemistry testing on "10

[14] There were no mortalities during the study. SER83.

rodents of each sex per group at least three times during the study"); ER274 (suggesting that "urine volume collection should be conducted during the last week of the study on at least 10 animals of each sex in each group"). It is entirely reasonable for FDA to have relied on a study that ultimately produced data sufficient to satisfy the agency's guidance for obtaining meaningful results.

B. FDA Considered Effects Observed During The Feeding Study And Reasonably Explained Why Those Effects Did Not Warrant Further Investigation.

Next, the Center argues that FDA unreasonably dismissed observations related to blood proteins and other physiological responses during the Feeding Study because those statistically significant differences occurred in only one sex. Center Br. 55. That is not an accurate characterization of FDA's reasoning. And the Center's assertion that the Feeding Study's design meant that FDA could not adequately consider the import of the observed effects, *id.*, is merely a repackaging of its prior arguments and fails for the same reasons.

1. In its objections to FDA, the Center argued that data from the Feeding Study revealed statistically significant changes in some clinical values compared to controls. ER5, ER16. Citing an online report, the Center suggested that these differences required further investigation by FDA. *See* ER5, ER16. FDA explained in response that "differences in observed clinical chemistry parameters, even if statistically significant, do not necessarily mean that treatment-related

differences exist." ER5. Here, FDA concluded "that the statistically significant differences were incidental and not treatment-related." *Id.* FDA explained that "[t]he available information on the structure and function of soy leghemoglobin and its fate in the body following consumption do not lend support to the Center['s] claim that the statistically significant differences reported in the study are indicative of potentially adverse effects in humans." *Id.*

The Center's claim notwithstanding, Br. 55, FDA's conclusion was not based only on the lack of observed changes in both sexes. Instead, FDA cited "numerous accounts of historical control data" showing "that certain clinical chemistry parameters may have a wide range of normal values . . . , such that statistical differences seen between control animals and treatment animals due to small changes in the value of the parameter are not likely to be of biological or toxicological significance." ER5. Here, FDA explained, "the changes observed for these parameters in Impossible Food's 28-day study were within historical ranges of control values, did not show a dose-response relationship, *and* did not occur in both sexes." *Id.* (emphasis added). Thus, FDA relied on several considerations to conclude that the Center's "objection is based purely on statistical significance and not biological significance or toxicological relevance." *Id.* And while FDA did consider differences in changes between sexes as part of its calculus, the Center points to no rule, regulation, or guidance document that

suggests such a consideration is improper in conjunction with other considerations. *See* Center Br. 55. And that observation is consistent with FDA's mandate to assess whether differences are *caused by* soy leghemoglobin consumption, which both sexes are consuming.

2. The Center's fallback argument is to claim that "FDA cannot determine statistically significant effects are merely 'incidental' based upon such a small sample size." *Id.* This argument is new on appeal, and therefore forfeited. *See Koretoff*, 707 F.3d at 398.

In any event, this argument contains a familiar fatal defect: FDA's *suggestions* that subchronic toxicity studies have 20 rats per sex per group and go on for 90 days are not *requirements*. *Supra* pp. 36-39. And the Redbook fully supports FDA's ability to evaluate the effects observed during the Feeding Study. FDA explained why a longer study would have no utility, *supra* p. 37, and the purpose of the Redbook's suggestions regarding sample size is to ensure there are enough animals to conduct "a meaningful evaluation of toxicological effects," ER268. How many animals is that? Generally, ten. *See supra* pp. 38-39. Thus, the Feeding Study aligns with the guidelines recommended by the Redbook for adducing sufficient data "to permit a meaningful evaluation of toxicological effects." ER268. The Center's claim to the contrary has no merit, and courts generally defer "[w]hen, as in this case, the agency 'is making predictions, within

its area of special expertise, at the frontiers of science." *NRDC*, 857 F.3d at 1036 (quoting *NRDC*, 735 F.3d at 877).

C. FDA's Decision Is Supported By Substantial Evidence Even Setting Aside The Feeding Study.

The Center's myopic focus on the Feeding Study also ignores the full spectrum of additional evidence FDA considered in concluding that soy leghemoglobin is safe. As FDA explained in its response to the Center's objections to the final rule, its "safety evaluation for a color additive considers the additive's manufacturing; its 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." ER4.

FDA further explained that it had considered Impossible's weight-of-evidence approach to its product safety analysis, which it considered "a widely used method for assessing protein safety by experts in the scientific community." ER3. That review considered: (1) the long history of safe human consumption of soy, soy leghemoglobin protein, and *P. pastoris*; (2) the safety of the genetically engineered *P. pastoris* production strain; (3) a 14-day range-finding feeding study and a study to address the estrous cycle distribution observed during the Feeding Study; (4) studies showing no mutagenicity and genotoxicity of the soy leghemoglobin preparation; and (5) an allergenicity assessment concluding soy

leghemoglobin and *P. pastoris* are unlikely to prove allergenic. *Supra* pp. 9-12, 34. And before approving soy leghemoglobin, FDA had its own scientists review the totality of the evidence submitted by Impossible. *See* ER289-299; ER320-335.

The Center simply ignores these other components of the agency's decision, which in themselves are more than sufficient to satisfy the "substantial evidence" threshold. *NRDC*, 857 F.3d at 1036 ("Substantial evidence . . . is such relevant evidence as a reasonable mind might accept as adequate to support a conclusion . . . even if it is possible to draw two inconsistent conclusions from the evidence.").[15]

IV. VACATUR IS NOT THE APPROPRIATE REMEDY FOR ANY DEFECTS IN THE LISTING.

If, despite all this, the Court were to find a procedural defect in the decision or a basis for FDA to need to further explain its rationale, the appropriate course would be remand without vacatur. "When determining whether to leave an agency action in place on remand, [this Court] weigh[s] the seriousness of the agency's errors against 'the disruptive consequences of an interim change'" while the agency reconsiders. *Pollinator Stewardship Council v. EPA*, 806 F.3d 520, 532 (9th Cir. 2015).

[15] The Center likewise did not present to FDA its suggestion (at 50-51) that a chronic toxicity study was required. *See* ER14-16. That argument, too, is forfeit. *Koretoff*, 707 F.3d at 398.

In this case, vacatur would be highly disruptive. The alleged errors the Center highlights—if they are errors at all—are highly technical and easily corrected, making it very "likely . . . [FDA] could adopt the same rule on remand." *Id.* Meanwhile, Impossible's products are widely available in restaurants and supermarkets across the country, and the Center points to precisely zero evidence of a single customer experiencing an adverse health effect (which, again, is part of why it has no standing). Under these circumstances, there is no reason to vacate the decision pending the agency's reconsideration.

CONCLUSION

For the foregoing reasons, the petition should be dismissed for lack of jurisdiction, or else denied.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) and Ninth Circuit Rule 32-1(a) because it contains 9,916 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the typestyle requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Office Word 2010 in Times New Roman 14-point font.

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CERTIFICATE OF SERVICE

I certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF system on November 23, 2020. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

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