No. 17-13376

IN THE UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

UNDETERMINED QUANTITIES OF ALL ARTICLES OF FINISHED AND IN-PROCESS FOODS, raw ingredients (bulk powders, bulk capsules), with any lot number, size, or type container, whether labeled or unlabeled, et al.,

Defendants,

and

HI-TECH PHARMACEUTICALS, INC. and JARED WHEAT,

Claimants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF GEORGIA

BRIEF FOR THE UNITED STATES

Of Counsel:

ROBERT P. CHARROW
General Counsel

REBECCA K. WOOD
Chief Counsel, Food and Drug Division

ANNAMARIE KEMPIC
Deputy Chief Counsel, Litigation

JOSHUA A. DAVENPORT
Associate Chief Counsel

U.S. Food and Drug Administration

CHAD A. READLER
Acting Assistant Attorney General

BYUNG J. PAK
United States Attorney

SCOTT R. McINTOSH
DANIEL AGUILAR
Attorneys, Appellate Staff
Civil Division, Room 7266
U.S. Department of Justice
950 Pennsylvania Ave., NW
Washington, DC 20530
(202) 514-5432

CERTIFICATE OF INTERESTED PERSONS AND CORPORATE DISCLOSURE STATEMENT

Pursuant to 11th Cir. R. 26.1-1, the undersigned counsel certifies that, to the best of our knowledge, the following persons and entities may have an interest in the outcome of this case, in addition to those people and entities listed in the certificate included in claimants-appellants' opening brief (filed November 22, 2017):

Bruce Harvey Law Firm

Charrow, Robert P.

Clark, Andrew E.

Cohen, Leslie

Davis, Jeffrey S.

Delery, Stuart F.

Dotzel, Margaret M.

Frimpong, Maame Ewusi-Mensah

Gorji, Perham

Law Office of Bruce Harvey

Mizer, Benjamin C.

McIntosh, Scott R.

Morton, Lakisha N.

Olin, Jonathan F.

Pak, Byung J.

Readler, Chad A.

Schultz, William B.

Sills Cummis & Gross P.C.

United States Department of Justice

Wood, Rebecca K.

Yates, Sally Quillian

I further certify that, to the best of my knowledge, no publicly traded company or corporation has an interest in the outcome of this case or appeal.

/s/ Daniel Aguilar
Daniel Aguilar
Counsel for the Appellee

STATEMENT REGARDING ORAL ARGUMENT

The district court's decision should be affirmed for the reasons stated by the district court. The government stands ready to present oral argument at the Court's request.

TABLE OF CONTENTS

Page

TABLE OF CITATIONS*

Cases: **Page(s)**

* Authorities upon which we primarily rely are marked with asterisks.

Statutes:

Rules and Regulations:

Legislative Material:

Other Authorities:

STATEMENT OF JURISDICTION

The district court had jurisdiction under 21 U.S.C. § 334 and 28 U.S.C. § 1345. Doc. 25 at 3. The district court granted summary judgment in favor of the United States on April 3, 2017. Doc. 140 at 13-14. Appellants moved for reconsideration of that order on April 17, 2016 (Doc. 142), and the district court denied reconsideration on June 2, 2017 (Doc. 148 at 3). Appellants filed a notice of appeal on July 26, 2017. Doc. 149. This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

Appellants sell weight-loss and energy-enhancement products that contain the chemical 1, 3-Dimethylamylamine, commonly called DMAA. The United States seized those products, and the district court ordered them to be condemned for destruction because DMAA is an unsafe food additive that renders the products adulterated under the Federal Food, Drug, and Cosmetic Act.

The issues presented are:

1. Is DMAA a dietary ingredient or a food additive, as those terms are defined in the Federal Food, Drug, and Cosmetic Act?

2. Is DMAA generally recognized as safe by experts qualified by scientific training and experience to evaluate the safety of substances added to food?

STATEMENT OF THE CASE

I. STATUTORY AND REGULATORY FRAMEWORK

A. The Food and Drug Administration (FDA) is charged by Congress to "protect the public health by ensuring that * * * foods are safe, wholesome, sanitary, and properly labeled." 21 U.S.C. § 393(b)(2)(A). The Federal Food, Drug, and Cosmetic Act (the Act) prohibits the introduction of adulterated foods into interstate commerce. *Id.* § 331(a). The United States may initiate an *in rem* forfeiture action in district court to seize and condemn adulterated foods. *Id.* § 334(a)(1). A person with an interest in the foods may file a claim of interest and contest the forfeiture action, Fed. R. Civ. P. Supp. R. G(5)(a)(i), including by arguing that the foods are not adulterated. FDA may also administratively detain foods found during its routine inspections and investigations if it has reason to believe that the foods are adulterated. 21 U.S.C. § 334(h) (authorizing administrative detentions of up to 30 days).

A food is deemed to be "adulterated" under the Act if, *inter alia*, it contains "any food additive that is unsafe." 21 U.S.C. § 342(a)(2)(C)(i). Food additives are generally "deemed to be unsafe" unless a regulation specifically permits their use. *Id.* § 348(a).

B. "Food additives" are generally defined as substances that are (1) intended to be part of food or affect the characteristics of food; and (2) "not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures * * * to be safe under the

conditions of its intended use." 21 U.S.C. § 321(s). This brief refers to the second part of this definition by the shorthand phrase "not generally recognized as safe by scientific experts."

Excluded from the statutory definition of "food additive" are dietary ingredients that are "in, or intended for use in, a dietary supplement." 21 U.S.C. § 321(s)(6). As relevant here, the Act defines "dietary supplement" as a product (besides tobacco) that is "intended to supplement the diet" and that contains one or more of the following "dietary ingredients":

> (A) a vitamin;
> (B) a mineral;
> (C) an herb or other botanical;
> (D) an amino acid;
> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

Id. § 321(ff)(1). Dietary supplements are considered food. *Id.* § 321(ff).

C. Food additives and dietary ingredients are regulated differently under the Act. Among other things, in an action to seize and condemn adulterated foods containing unsafe food additives, the claimant bears the burden of proving that the alleged unsafe food additive is generally recognized as safe by scientific experts—and therefore does not cause the food to be adulterated. *United States v. 45/194 Kg. Drums of Pure Vegetable Oil*, 961 F.2d 808, 812 (9th Cir. 1992) (citing *United States v. An Article of Food*, 752 F.2d 11, 15 (1st Cir. 1985)); *United States v. An Article of Food*, 678 F.2d 735,

739 (7th Cir. 1982). By contrast, in an action to seize and condemn dietary supplements, the government bears the burden of proving that the supplement is adulterated. 21 U.S.C. § 342(f)(1). Dietary supplements are considered adulterated if it contains a dietary ingredient that "presents a significant or unreasonable risk of illness or injury" under recommended or ordinary conditions of use. *Id.* § 342(f)(1)(A).[1]

II. FACTUAL BACKGROUND AND PROCEDURAL HISTORY

A. The History of DMAA

DMAA is a chemical compound composed of a chain of carbon atoms that are bonded to groups of hydrogen, carbon, and nitrogen atoms. Doc. 107-6 at 6-7, Doc. 107-7 at 18. DMAA was invented by Eli Lilly & Co., which synthesized the compound and patented it in 1944. Doc. 107-4 at 3.[2] Eli Lilly described DMAA as a chemical that "possess[es] the desirable properties of both ephedrine and

[1] A dietary supplement may also be adulterated if it contains a new dietary ingredient for which there is "inadequate information to provide reasonable assurance" that the dietary ingredient does not present a significant or unreasonable risk of injury; the Secretary of Health and Human Services declares the supplement or one of its dietary ingredients to "pose an imminent hazard to public health or safety;" or the supplement bears or contains a poisonous or deleterious substance that may render the product injurious to health. 21 U.S.C. § 342(f)(1)(B)-(D).

[2] Eli Lilly's patent identifies DMAA by the chemical name 2-amino-4-methylhexane. Doc. 107-4 at 3. Other chemical names for DMAA include 1,3-dimethylamylamine, 1,3-dimethylpentylamine, 4-methylhexan-2-amine, 2-hexanamine, methyl hexane amine methylhexamine, methylhexanamine, and pentylamine. Doc. 107-6 at 11-12; Doc. 108-4 at 37.

amphetamine." *Id.* Prior to Eli Lilly's patent, DMAA had not been discussed in any scientific literature. Doc. 107-6 at 3. DMAA was used in a nasal decongestant drug called Forthane, 37 Fed. Reg. 13,488, 13,491 (July 8, 1972), until FDA withdrew Forthane's approval at the manufacturer's request in 1983, 48 Fed. Reg. 51, 533, 51,536 (Nov. 9, 1983).

In the last ten years, DMAA began to appear in products that claimed to promote weight loss, bodybuilding, and athletic performance. Doc. 107-5 at 175. In 2011, four U.S. soldiers died after exercising and were found to have traces of DMAA in their blood. *Id.* at 165. As a precautionary measure, the Department of Defense ordered all products that contained DMAA to be removed from military exchanges and concession stores on military installations, pending further review. *Id.* In that review, the Department of Defense issued a report that evaluated self-reported data from thousands of soldiers about their DMAA use and particular health problems (*e.g.*, cardiac dysrhythmia and seizures). *Id.* at 193. While the report could not identify a direct relationship between DMAA and health problems, it did find that—among soldiers with health problems—those who had multiple health problems in the last year were twice as likely to have used DMAA. *Id.* at 211. And the more often those soldiers used DMAA over a prolonged period of time, the more likely they were to have had multiple health problems (at a statistically significant level). *Id.* The report concluded that further studies were needed to "look more closely at the health effects of exposure to DMAA in terms of frequency and amount," and to "examine specific

outcomes, such as heat injuries and rhabdomyolysis." *Id.* The report further recommended the Department of Defense continue to prohibit the sale of DMAA-containing products on military instillations, explaining that "the evidence supports sufficient risk, even if very low, of another death or catastrophic illness of a Service member who has used DMAA-containing products, without any offsetting benefit." *Id.* at 172.

B. The United States Seizes Hi-Tech's Products Containing DMAA

In 2013, FDA employees conducted an inspection of facilities owned by appellant Hi-Tech Pharmaceuticals, Inc., during which the employees saw products that contained DMAA. Doc. 25 at 5-6; Doc. 26 at 3-4. After the inspection, FDA administratively detained the products that contained DMAA, and the United States subsequently filed a complaint in the Northern District of Georgia seeking forfeiture of those products. Doc. 25 at 5-6. The complaint alleged that DMAA is not a dietary ingredient but a food additive, and that DMAA is not generally recognized as safe by scientific experts. Doc. 1 at 5. Accordingly, the United States sought to seize and condemn the products containing DMAA as adulterated foods, (*id.* at 6 (citing 21 U.S.C. § 334)), and the district court issued a warrant authorizing the U.S. Marshals to seize the products pending a judgment (Doc. 2 at 2-3). Hi-Tech Pharmaceuticals and its sole shareholder Jared Wheat (collectively, Hi-Tech) claimed an interest in the products and disputed that they were adulterated. Doc. 11 at 2.

Soon after the products were administratively detained by FDA and before the seizure action was filed, Hi-Tech filed a complaint in the District Court for the District of Columbia, seeking a declaration that the detention of its products violated the Fifth Amendment's Due Process Clause and the Administrative Procedure Act. Doc 41-1. That complaint was transferred to the Northern District of Georgia and merged with the United States' seizure action. Doc. 29 at 1-2.

C. The District Court Grants Summary Judgment to the United States

1. The parties filed cross-motions for summary judgment. The United States argued that DMAA is an unsafe food additive under 21 U.S.C. §§ 321(s), 348(a), because there is no general consensus among scientific experts that DMAA is safe for human consumption, Doc. 107-1 at 13, 23-32.

In contrast, Hi-Tech argued that DMAA qualified as a dietary ingredient under 21 U.S.C. § 321(ff)(1)(F), and therefore was not a food additive, because it was a "constituent and/or extract of a botanical." Doc. 108-1 at 21. Specifically, Hi-Tech argued that some scientific studies had detected DMAA in geranium plants, and that the alleged presence of DMAA in geraniums renders it a constituent or extract of a botanical. *Id.* As a dietary ingredient, Hi-Tech continued, there was no genuine dispute of material fact about whether DMAA "presents a significant or unreasonable risk of illness or injury" under conditions of normal or recommended use. *Id.* at 22 (citing 21 U.S.C. § 342(f)(1)(A)). Based on those predicates, Hi-Tech argued that the

United States did not have statutory authority to seize and condemn its products. Doc. 108-1 at 19.

The parties disputed whether scientific studies had reliably detected DMAA in geraniums. Hi-Tech relied on two studies—the Fleming study and the Li study—that detected DMAA in geraniums at trace levels, from 14 parts per billion to 365 parts per billion. Doc. 119-1 at 21, 26. In other words, the studies claimed to detect DMAA at levels that would require somewhere between 2.74 to 71.43 metric tons of geraniums to produce 1 gram of DMAA. Hi-Tech recommends between 45 and 135 milligrams of DMAA for a single day's use. Doc. 108-4 at 31; Doc. 108-8 at 114-15. Using the highest levels of DMAA concentration found in Hi-Tech's studies (assuming they were accurate and valid), it would take at least 123 kilograms (271 pounds) of geraniums to manufacture a single 45 milligram pill of DMAA.[3]

[3] The Li study also detected DMAA in three "geranium oil samples [that] were obtained from Jiangxi Ji'an Hengcheng Flavor Oil Factory." Doc. 108-5 at 36. In two oil samples, the Li study detected DMAA in concentrations similar to the levels it detected in geranium plants. *Id.* at 43. The third oil sample contained DMAA at levels approximately 100 to 1,000 times greater than those found in any other plant or oil samples. *Id.* The Li study suggested that this anomaly may be caused by "either different geranium plants used for oil processing or from different manufacturing processes." *Id.*

Hi-Tech also cites a 1996 study by Ping *et al.* as evidence that DMAA has been detected in geraniums. *See* Opening Br. 13 (citing Doc. 108-7 at 407-12). When Hi-Tech's experts were deposed, however, they could not show where the Ping study discussed DMAA, or at what levels DMAA had been detected. Doc. 107-5 at 12-15, 66-67.

The United States pointed to other studies that had not detected DMAA in geraniums (Doc. 107-6 at 4, 27), and argued that the Li and Fleming studies detecting DMAA in geraniums were flawed and produced results inconsistent with other observed data. One of the authors of the Fleming study created a solution of DMAA and water that had a similar concentration of DMAA to the levels that had been reported in geraniums. Doc. 107-5 at 23, 27, 53-57. The author then watered geraniums with this solution, and the geraniums almost died as a result. *Id.* at 53. The Fleming study's author had no explanation for why, if geraniums produced low levels of DMAA naturally, a geranium could not process similar levels of DMAA in water. *Id.* at 57-59. The author, along with Hi-Tech's other experts, also could not explain how a geranium could naturally produce DMAA through a biologically plausible mechanism. *Id.* at 9, 41-42, 94-95.

The United States also identified a potential source of contamination that could explain the presence of DMAA in geraniums treated with commercial fertilizer. One brand of fertilizer was found to contain DMAA at concentration levels of 12 parts per billion (Doc. 107-5 at 48-50), near the low end of the DMAA levels that had been detected in geraniums (Doc. 119-1 at 21). If a geranium were grown with a fertilizer that contained DMAA, the chemical might be absorbed into a plant through its roots. Doc. 107-5 at 51-52. Neither the Fleming study nor the Li study examined whether the geraniums they analyzed had been grown with fertilizers that contained DMAA. *Id.* at 51-52, 151-53.

2. The district court did not resolve the factual dispute over whether DMAA occurs naturally in geraniums. Although the court stated that it "would be inclined to find that the Government has failed to meet its burden of establishing that DMAA has not been found in geraniums", it declined to do so at summary judgment. Doc. 140 at 7. Instead, the district court explained that even if geraniums naturally produce DMAA (or DMAA could otherwise be found in geraniums), the statutory question of whether DMAA is a constituent of a botanical under 21 U.S.C. § 321(ff) remained. Doc. 140 at 7.

In answering that question, the district court construed the term "botanical" to mean a substance that has been "extracted from a plant or plant-like organism and used, for example, in or as a medicine." Doc. 140 at 8. The district court noted that, in normal usage, botanical refers to "a plant, a part of a plant, or a substance that is derived from a plant for a medicinal, cosmetic, or other purpose." *Id.* at 7-8. The court cited dictionary definitions of botanical to mean "[a] substance obtained from a plant" and "a drug made from part of a plant, as from roots, leaves, bark, or berries." *Id.* at 8.

Applying that statutory construction to this case, the district court held that DMAA did not qualify as a dietary ingredient under 21 U.S.C. § 321(ff) because "the DMAA in the marketplace has *never* been extracted from geraniums or any other plant," but had only been produced by synthetic means. Doc. 140 at 8. The court opined that a botanical chemical could be synthesized in a lab and still qualify as a

dietary ingredient under 21 U.S.C. § 321(ff). Doc. 140 at 8. But there "must be at least some history of the substance in question having been extracted in usable quantities from a plant or a plant-like organism" in order for it to be considered a botanical at all. *Id.* at 9.

The court found further support in the congressional purpose behind the Act and its amendments. As noted above, dietary supplements and dietary ingredients are subject to more lenient premarket regulatory requirements than food additives. *Compare* 21 U.S.C. § 342(f)(1)(A), *with id.* §§ 342(a)(2)(C)(i) *and* 348(a). The district court found it implausible that Congress intended to allow manufacturers to claim the benefit of the relaxed regulatory regime for dietary supplements by synthesizing "a chemical that heretofore had only been manufactured in a laboratory," then launching a worldwide quest to discover a plant that happens to contain the chemical in "miniscule amounts." Doc. 140 at 8-9. "To hold otherwise would be to open the door to bogus claims that, for example, a given chemical had been detected in a fungus found only in a remote Tibetan river valley, and FDA would be left to refute that claim—to prove a negative—which the instant case demonstrates is not easily done." *Id.* at 9.

3. Having determined that DMAA did not qualify as a dietary ingredient under 21 U.S.C. § 321(ff), the district court next examined whether DMAA was generally recognized as safe by scientific experts. Doc. 140 at 9-10. After reviewing the parties' scientific reports, the court concluded that "there is no consensus regarding the

question of whether the consumption of DMAA is safe." *Id.* at 11. The court noted that scientific experts had "raised legitimate concerns regarding the safety of DMAA," *id.*, and while Hi-Tech had pointed to some studies that showed DMAA was not associated with significant adverse effects, the sample size of those studies was "simply too small to provide any convincing evidence" about DMAA's safety, *id.* at 12. The district court concluded that Hi-Tech "failed to present sufficient evidence to demonstrate [a] consensus [among experts regarding DMAA's safety], leading to the further conclusion that DMAA is not generally recognized as safe under the [Act]." *Id.*

Accordingly, the court granted summary judgment to the United States, holding that DMAA was an unsafe food additive that rendered Hi-Tech's products containing DMAA adulterated and subject to seizure and condemnation under 21 U.S.C. § 334. Doc. 140 at 12-13. Having found forfeiture to be appropriate, the court also granted the United States summary judgment on Hi-Tech's claims that the seizure violated the Administrative Procedure Act and the Due Process Clause of the Fifth Amendment. *Id.*

4. Hi-Tech moved for reconsideration of the summary judgment order on two primary grounds. First, Hi-Tech argued that the court erroneously only considered whether DMAA was a botanical, rather than whether it was a constituent of a botanical. Doc. 142 at 14-21. Second, Hi-Tech argued that it should be permitted to

introduce new evidence to demonstrate that DMAA can be extracted from geraniums in usable amounts. *Id.* at 22-24.

The district court denied reconsideration. Doc. 148 at 3. The court first explained that "a botanical—and by extension, a constituent of a botanical—is something that comes from a plant, and none of the DMAA ever placed in a product for sale has come from a plant." *Id.* at 2. Second, the court explained that new evidence was unnecessary because even the evidence Hi-Tech proffered only discussed the hypothetical potential to extract DMAA from geraniums. *Id.* That potential evidence, however, would not demonstrate that DMAA had in fact been extracted from geraniums for use in a product. *Id.* at 2-3. If there were such evidence, "there would not have been a dispute regarding whether DMAA was a botanical in the first instance." *Id.* at 3.

III. STANDARD OF REVIEW

"This court reviews a district court's grant of summary judgment de novo." *Hi-Tech Pharm., Inc. v. Crawford*, 544 F.3d 1187, 1189 (11th Cir. 2008) (per curiam). Summary judgment is appropriate when there are no genuine issues of material fact and when the moving party is entitled to judgment as a matter of law. *Id.*

SUMMARY OF ARGUMENT

I. DMAA is a food additive, not a dietary ingredient. The district court correctly construed the statutory terms in 21 U.S.C. § 321(ff)(1) to mean that a "constituent" of a "botanical" is a substance that is physically derived from a plant,

not merely a substance that is claimed to be present in the plant in trace amounts but has never been obtained from it. The district court's interpretation is supported by the dictionary definitions of the relevant statutory terms, applicable canons of statutory construction, and Congress's understanding when it enacted that statutory provision. Each of these sources confirms that when the statute refers to a "constituent" of a "botanical," it means something that has been physically derived from a plant. DMAA does not fit this description and therefore does not qualify as a dietary ingredient under § 321(ff)(1); rather, DMAA meets the definition of a food additive under § 321(s).

II. The district court correctly concluded that DMAA is not generally recognized as safe by scientific experts, and therefore is an unsafe food additive. 21 U.S.C. § 321(s). The summary judgment record included many studies documenting health risks posed by consumption of DMAA, and even Hi-Tech's experts agreed that further study was necessary to evaluate DMAA's effects on people's health. While Hi-Tech proffered some studies that did not find negative health effects under certain conditions of testing, the district court rightly concluded that there was no factual basis to conclude that scientific experts generally recognize DMAA as safe—*i.e.*, it was not "common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food" that DMAA is safe for use as intended. 21 C.F.R. § 170.30(a).

ARGUMENT

I. DMAA IS NOT A DIETARY INGREDIENT BECAUSE IT IS NOT A BOTANICAL OR A CONSTITUENT OF A BOTANICAL

The district court sustained the government's *in rem* forfeiture action under the Federal Food, Drug, and Cosmetic Act because DMAA is an unsafe food additive that renders Hi-Tech's products adulterated. In so doing, the district court correctly construed the statutory definitions in 21 U.S.C. § 321(ff) to conclude that DMAA is not a dietary ingredient and hence is not excluded from the Act's definition of a food additive under 21 U.S.C. § 321(s)(6).

The parties agree that DMAA is not a vitamin, mineral, or an amino acid. Doc. 119-1 at 6. The central dispute is whether DMAA is an "herb or other botanical" or a "constituent" of an herb or a botanical. 21 U.S.C. § 321(ff)(1). Because these statutory terms are not further defined by the Act, the Court construes them "in accordance with [their] ordinary meaning," *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 134 S. Ct. 1749, 1756 (2014), and by using the usual tools of statutory construction. To determine whether DMAA is a "botanical" or a "constituent" of a botanical, the Court should look to how those terms are used and how those terms were understood by Congress at the time of their enactment into § 321(ff)(1).

A. Definitions and Canons of Statutory Construction

The statutory issue is whether a substance must have been physically derived from a plant in order to qualify as a "constituent" of a "botanical" under 21 U.S.C.

§ 321(ff). The dictionary definitions of both terms—"botanical" and "constituent"—point strongly in favor of the district court's construction, as do the definitions of the other relevant terms in § 321(ff).

Both "herb" and "botanical" are defined to mean either a plant itself or a part physically taken from a plant. Herb is defined as "a plant or a plant part valued for its medicinal, savory, or aromatic qualities," while botanical is defined as an item "derived from plants" or "a plant part or extract." *Merriam-Webster's Collegiate Dictionary* 134, 542 (10th ed. 1998) (*Merriam-Webster*).[4] Those definitions are consistent with the district court's holding that DMAA must be derived from a plant in order to qualify as a botanical. Doc. 140 at 8 (citing similar definitions from the Oxford Dictionary and Dictionary.com).

"Constituent," in turn, is defined to mean "an essential part" and identifies "element" as a synonym. *Merriam-Webster* 248.[5] The definition of "element," in turn, casts further light on the meaning of "constituent."

---

[4] *Merriam-Webster's Collegiate Dictionary* has been relied upon by the Supreme Court and by this Court to discern the ordinary meaning of English words. *Octane Fitness*, 134 S. Ct. at 1756 (citing *Merriam-Webster*); *Burlington N. & Santa Fe Ry. Co. v. United States*, 556 U.S. 599, 611 (2009) (same); *United States v. Zuniga-Arteaga*, 681 F.3d 1220, 1224 (11th Cir. 2012) (same); *Arriaga v. Florida Pac. Farms, LLC*, 305 F.3d 1228, 1242 (11th Cir. 2002) (same). The dictionary's tenth edition was published in 1998, close in time to the congressional amendments to the Act that created 21 U.S.C. § 321(ff). *See* Pub. L. No. 103-417, § 3(a), 108 Stat. 4325, 4327 (1994).

[5] "Constituent" also has unrelated meanings that have no relevance to the statutory text, such as a member of a constituency or a structural unit of language. *Merriam-Webster* 248.

> **Element** * * * **2** * * * **f :** a distinct part of a composite device. * * * ***Syn*** ELEMENT, COMPONENT, CONSTITUENT, INGREDIENT mean one of the parts of a compound or complex whole. * * * COMPONENT and CONSTITUENT may designate any of the substances (whether elements or compounds) or the qualities that enter into the makeup of a complex product; COMPONENT stresses its separate entity or distinguishable character <the *components* of a stereo system>. CONSTITUENT stresses its essential and formative character <the *constituents* of a chemical compound>.

Id. at 373.

This definition of "constituent" aligns well with the district court's holding. DMAA was invented and patented by Eli Lilly as a new chemical compound over fifty years before anyone purported to identify it in a particular plant species. *Compare* Doc. 107-4 at 3 (DMAA patented by Eli Lilly in 1944), *with* Doc. 108-1 at 33 (Hi-Tech's reliance on a 1996 study stating that it detected DMAA in geraniums). Even taking the studies cited by Hi-Tech at face value, DMAA is present in geraniums in trace amounts that are so low as to be nearly undetectable, and it has never been physically derived from a geranium. In these circumstances, there is no sense in which DMAA can be said to be an "essential and formative" part of a botanical—it was invented by humans and has never been derived from a botanical. *See also* Food & Drug Admin., U.S. Dep't of Health & Human Servs., *Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* 76 (July 2011 Draft), available for download at https://www.regulations.gov/document?D=FDA-2011-D-0376-0002 (defining constituent as "[a]n article that is a physical part of the whole and *can be isolated* from the whole" (emphasis added)). Accordingly, the district court was

correct to conclude that DMAA is not a constituent of a botanical when it has never been obtained from a botanical.

Notably, the statutory text does not use the term "constituent" in isolation, but in a series of words to explain what qualifies as a dietary ingredient. The statute defines dietary ingredients to include any "concentrate, metabolite, constituent, extract, or combination" of vitamins, minerals, herbs or other botanicals, and amino acids.[6] 21 U.S.C. § 321(ff)(1)(F). Because the statute presents "constituent" in a series of closely associated words, the canon of *noscitur a sociis* applies—the meaning of "constituent" is informed by the meaning of the associated words in the statutory list. *In re Piazza*, 719 F.3d 1253, 1263 n.4 (11th Cir. 2013) (discussing *noscitur a sociis*); Antonin Scalia & Bryan A. Garner, *Reading Law: The Interpretation of Legal Texts* 195 (2012) (*Reading Law*) (same). The "most common effect of the canon is not to establish which of two totally different meanings applies but rather to limit a general term to a subset of all the things or actions that it covers." *Reading Law* 196.

Applying *noscitur a sociis*, the associated words inform the meaning of "constituent" because they all refer to physical processes of obtaining or creating an item. A "concentrate" is a material that physically concentrates the essential elements

[6] Although not relevant here, a dietary ingredient also includes "a dietary substance for use by man to supplement the diet by increasing the total dietary intake." 21 U.S.C. § 321(ff)(1)(E).

of another substance (*e.g.*, orange juice concentrate).[7] An "extract" is a material physically extracted from another substance (*e.g.*, vanilla extract).[8] A "combination" is a material physically combined from two other substances.[9] And while it is more of a technical term, a "metabolite" refers to a material that is physically (*i.e.*, biochemically) produced as part of an organism's metabolic process.[10]

Like its associated words, "constituent" must refer to a material that can be derived through a physical process from a vitamin, mineral, herb, botanical, or amino acid. Although "constituent" could broadly be understood to mean *anything* that is contained in a larger substance, that broad meaning would not be consistent with the common uses of the other words in § 321(ff)(1)(F), all of which connote derivation through physical processes.

Hi-Tech's open-ended construction of "constituent" to simply mean "[o]ne part of something" (Opening Br. 47), is comparable, for example, to the word "uses,"

---

[7] *See Merriam-Webster* 238 ("**Concentrate** * * * **1:** something concentrated: as **a:** a mineral-rich product obtained after an initial processing of ore **b:** a good reduced in bulk by elimination of fluid <orange juice>.").

[8] *See Merriam-Webster* 412 ("**Extract** * * * **2:** a product (as an essence or concentrate) prepared by extracting; *esp*: a solution (as in alcohol) of essential constituents of a complex material (as meat or an aromatic plant).").

[9] *See Merriam-Webster* 228 ("**Combination** * * * **1 a:** a result or product of combining * * * **5 a:** the act or process of combining; *esp:* that of uniting to form a chemical compound **b:** the quality or state of being combined.").

[10] *See Merriam-Webster* 730 ("**Metabolite** * * * **1:** a product of metabolism **2:** a substance essential to the metabolism of a particular organism or to a particular metabolic process.").

which could be understood to have a broad meaning encompassing every conceivable type of utility. But in a statute that punishes a person who "transfers, possesses, or uses" another person's identification, the term "uses" "must have practical boundaries" that are informed by its associated words. *United States v. Miller*, 734 F.3d 530, 539, 541 (6th Cir. 2013) (construing 18 U.S.C. § 1028A(a)(1)). Similarly, one could broadly construe the word "case" (in the sense of a container) to include a purse, since a purse is capable of being held and holding objects. But in a statute that permits guns in automobiles only if the gun is contained "in a closed and fastened case, gunbox, or securely tied package," a gun in a purse would not be permitted. *State v. Taylor*, 594 N.W.2d 533, 535-36 (Minn. Ct. App. 1999). The statute's accompanying references to "gunbox" and "securely tied package" made clear that a "case" must be "a container that does not make the gun readily retrievable"—not a purse that may be easily opened. *Reading Law* 197 (discussing *Taylor*).

Likewise, the term "constituent" in § 321(ff)(1)(F) must have a more limited meaning informed by the other words in that subsection. And such a limited meaning—focusing on the physical processes for obtaining a material from another substance—supports the district court's statutory construction. To be a dietary ingredient, DMAA "must have been extracted from a plant or plant-like organism." Doc. 140 at 8.

Hi-Tech argues that a "constituent" of a botanical cannot be limited to a substance physically derived from a botanical because the statute already uses the

word "extract" to cover substances physically extracted from plants. Opening Br. 47-48. According to Hi-Tech, the district court's statutory construction would render the term "extract" superfluous, and therefore cannot be correct because Congress is presumed not to use superfluous words. *Id.* But the "canon against surplusage is not an absolute rule," and the canon is helpful only "where a competing interpretation gives effect to every clause and word of a statute." *Marx v. General Revenue Corp.*, 568 U.S. 371, 385 (2013). Hi-Tech broadly defines "constituent" to mean "[o]ne part of something" or a "component" of a larger thing. Opening Br. 47. But that broad sense of the word fails to give meaning to the terms "concentrate," "metabolite," and "extract" in 21 U.S.C. § 321(ff)(1)(F), each of which are a "part" or "component" of a larger thing. Orange juice concentrate consists of parts from oranges. A metabolite is a product of an organism's metabolism and can be found in that organism and is a part of it. And an extracted substance was clearly a part of the thing from which it was extracted. When "no interpretation of [the statute] gives effect to every word," the canon against surplusage is not dispositive. *Marx*, 568 U.S. at 385; *see also Reading Law* 176 ("Sometimes drafters *do* repeat themselves."). And to the extent the canon applies here, the district court's statutory construction should be preferred because it renders only one word arguably superfluous (constituent) compared to the three words that are rendered superfluous under Hi-Tech's interpretation (concentrate, metabolite, and extract).

In sum, the meanings of the relevant terms in 21 U.S.C. § 321(ff) support the district court's holding that a "constituent" of a "botanical" means a substance that is present in and actually derived from a plant. Under that standard, DMAA is not a constituent of a botanical.

B. Congressional Understanding

Statutory construction is informed by "the underlying policies of Congress and by common sense," both of which support the district court's conclusion. *Donovan v. Local 3122, Commc'n Workers of Am.*, 740 F.2d 860, 861 (11th Cir. 1984). In amending the Federal Food, Drug, and Cosmetic Act to add 21 U.S.C. § 321(ff) and its related provisions, Congress sought *inter alia* to clarify the line between food (including dietary supplements) and food additives. Congress believed that dietary supplements, like black currant oil, had wrongly been categorized as food additives by FDA. S. Rep. No. 103-410, at 21 (1994) (citing *United States v. Two Plastic Drums*, 984 F.2d 814, 815-16 (7th Cir. 1993) (holding that black currant oil—extracted from black currant berries—is food, not a food additive)). That classification matters because foods are presumed to be safe, while food additives are not. *Id.* Congress was concerned that without a clear statutory framework defining dietary supplements as food, dietary supplements might be presumed to be unsafe food additives, even though they were regularly used by "more than 100 million Americans." *Id.* at 6, 21-22.

Accordingly, Congress enacted 21 U.S.C. §§ 321(ff) and 342(f) to regulate dietary supplements that use botanicals "and their constituents," which "generally act

in a wider, more general, less specific way than most single-ingredient pharmaceutical drugs," by defining them as food and presuming them to be safe. S. Rep. No. 103-410, at 10. Hi-Tech contends that Congress's policy in enacting these statutes was to "open[] the dietary supplement category to an almost limitless variety of ingredients," which would all be presumed to be safe for human consumption. Opening Br. 48. Congress certainly intended to provide a different regulatory regime for botanicals and botanical products that people already consumed. But Hi-Tech points to nothing in the legislative history or common sense to suggest that Congress intended for a chemical compound like DMAA—a compound originally synthesized in a pharmaceutical lab that has never been derived from a plant for use in the human diet—to be presumed to be as safe as garlic or ginger. Instead, the district court's holding is consistent with the underlying logic of the line that Congress drew.

Botanicals and substances actually derived from botanicals properly enjoy the presumption of safety granted to foods by the Act, because people have historically consumed—and thus have evidence of the cumulative effect of consuming—botanicals and their derivatives like foods. But there is no reason why substances that have never been extracted from a plant for consumption—and that are present in plants (if at all) in levels so low that even scientific experts have difficulty detecting them—should enjoy that same presumption.

A contrary reading of the statutory scheme would undercut the framework that Congress established. As the district court recognized, Hi-Tech's statutory

construction would "open the door to bogus claims that, for example, a given chemical had been detected in a fungus found only in a remote Tibetan river valley," and was therefore a "constituent" of a "botanical" under § 321(ff) that is presumed to be safe for human consumption. Doc. 140 at 9. The United States would be left "to prove a negative," to demonstrate that the chemical did not, in fact, exist in any species of that fungus or plant. *Id.* There is always a chance that a scientific study will produce a false positive and detect something that does not actually exist. *See generally* Stephen E. Stein & David N. Heller, *On the Risk of False Positive Identification Using Multiple Ion Monitoring in Qualitative Mass Spectrometry*, 17 J. Am. Soc'y for Mass Spectrometry 823 (2006) (discussing false positives in identifying chemical compounds). And it may well be more in a dietary supplement company's financial interest to fund studies in the hope that a particular chemical may be found in a botanical, than it would be to fund clinical trials to demonstrate that a chemical is actually safe for human consumption. As the district court noted, "scientific studies performed on behalf of industry tend to produce the results that industry wants to see." Doc. 140 at 7.[11]

[11] Indeed, consistent and reliable evidence is integral to scientific research; otherwise, one or two outlier studies would be determinative. Studies that suggest a compound may be detectable in trace amounts may be inconsistent with other observed data and suffer from methodological flaws—in those circumstances, it would be wrong to view them as conclusive.

Requiring that a "constituent" of a botanical not merely be present in a plant at a parts per billion level, but actually be derived from a plant, is a vital safeguard against this kind of manipulation. If a substance is physically derived from a plant, it will necessarily have been demonstrated to be present in the plant.

C. Hi-Tech's Arguments to the Contrary Are Mistaken

To the extent that Hi-Tech has challenged the district court's statutory interpretation on textual grounds, we have addressed those arguments above. As we now show, Hi-Tech's remaining arguments are based on mistaken premises.

1. Hi-Tech complains that the district court's statutory construction cannot be correct because it would exclude chemicals like Pterostilbene (found in blueberries) and Resveratrol (found in grapes) from being considered dietary ingredients for use in supplements. Opening Br. 49. However, there are scientific studies that indicate these chemicals actually have been derived from plants. *See* Daniel M. Riche et al., *Analysis of Safety from a Human Clinical Trial with Pterostilbene* 2, Journal of Toxicology Article ID 463595 (2013) (describing a clinical trial where subjects consumed "a pterostilbene-rich extract" of the plant *Pterocarpus marsupium*); Dong-Geng Wang et al., *A Simple Method for the Isolation and Purification of Resveratrol from* Polygonum Cuspidatum, Journal of Pharmaceutical Analysis 241-46 (2013) (describing methods of deriving resveratrol from the plant *Polygonum cuspidatum*).

Furthermore, the sources cited by Hi-Tech suggest that Pterostilbene and Resveratrol are found in plants at concentration levels that are orders of dozens or

thousands of times larger than the levels at which DMAA has been detected in geraniums. *Compare* Doc. 119-1 at 21 (DMAA detected at 14 parts per billion to 365 parts per billion), *with* Opening Br. 49 (Pterostilbene detected at 10,000 parts per billion), *and id.* (citing Oregon State Univ. Linus Pauling Inst., *Micronutrient Information Center: Resveratrol* (2015) available at http://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/resveratrol) (Resveratrol detected at 14,300 parts per billion).

2. Hi-Tech contends that the district court's statutory construction is unnecessary as a policy matter to protect the public interest in food safety, because the marketing of any new dietary ingredients requires premarket notification by the manufacturer to FDA that the chemical is "reasonably * * * expected to be safe." Opening Br. 51 (citing 21 U.S.C. § 350b(a)(2)).[12] Yet Hi-Tech implicitly argues that this premarket notification requirement does not apply to DMAA, because the statute only applies to dietary ingredients marketed after October 15, 1994, and geraniums have been marketed for food uses before that date. *Id.* at 51-52. Hi-Tech's reading of the Act does not make sense. Under Hi-Tech's view, the hundreds of unknown organic compounds in geraniums (Opening Br. 13) would all be presumed to be safe for use in dietary supplements at much higher levels of concentration—regardless of

[12] Section 350b requires manufacturers or distributors of new dietary ingredients, or of dietary supplements that contain new dietary ingredients, to submit a premarket notification to FDA establishing that the new dietary ingredient will reasonably be expected to be safe, unless the new dietary ingredient has "been present in the food supply as an article used for food in a form in which the food has not been chemically altered." 21 U.S.C. § 350b(a)(1).

whether those organic compounds had ever been derived from botanicals or used for human consumption. Manufacturers of other substances could likewise point to the fact that their substance was present in trace amounts in a plant that had historically been part of the food supply—accordingly, they would contend, the substance had been marketed as a dietary ingredient before 1994, and 21 U.S.C. § 350b's requirements do not apply. Hi-Tech's proposed policy cure is no cure at all.

3. Hi-Tech asserts that the district court's judgment "exacerbate[s]" the alleged violations of the Administrative Procedure Act (APA) and 42 U.S.C. § 1983 that Hi-Tech asserted in its complaint against FDA, the Department of Health and Human Services, and the officials of those respective agencies. Opening Br. 52-54; *see also* Doc. 29 (order merging Hi-Tech's complaint with the United States' seizure action).

To begin with, Hi-Tech's complaint does not allege any claims under 42 U.S.C. § 1983, nor does it cite that statute. Doc. 41-1 at 1-21. Indeed, Hi-Tech cannot bring constitutional claims under § 1983 against the federal defendants named in its complaint because § 1983 only permits suits against state actors. *See generally Bivens v. Six Unknown Named Agents of Fed. Bureau of Narcotics*, 403 U.S. 388 (1971) (implying a cause of action against federal actors directly under the Constitution). Hi-Tech's complaint also does not allege any claims under *Bivens*, which would not be permitted for a variety of reasons. *See, e.g.*, *FDIC v. Meyer*, 510 U.S. 471, 484-86 (1994) (no *Bivens* actions against federal agencies); *Western Radio Servs. Co. v. U.S. Forest Serv.*, 578 F.3d 1116, 1122-23 (9th Cir. 2009) (no *Bivens* action when an APA action is available).

Additionally, all of the relief Hi-Tech sought in its complaint was directly related to stopping the United States' seizure action and obtaining a declaration and injunction that the United States may not lawfully seize products containing DMAA. Doc. 41-1 at 21. The district court rejected those claims by explaining why the United States was permitted to seize and condemn Hi-Tech's products containing DMAA, holding that they were adulterated under the Food, Drug, and Cosmetic Act because they contained unsafe food additives. Doc. 140 at 12-13. Hi-Tech criticizes the United States for seeking the condemnation of its products through an adjudication in federal court, rather than proceeding by rulemaking and regulation. Opening Br. 38-39, 57. But it is well established that when the federal government has a variety of permissible statutory and regulatory mechanisms available—such as proceeding by adjudication or by rulemaking—the government may use its discretion to choose among those options. *See RTC Transp., Inc. v. ICC*, 731 F.2d 1502, 1505 (11th Cir. 1984) (per curiam) ("It is well established, however, that agencies have discretion to choose whether to proceed by rulemaking or adjudication."); *see also Heckler v. Chaney*, 470 U.S. 821, 835 (1985) (explaining that 21 U.S.C. § 334 grants the United States permissive authority to seize adulterated products).

4. Hi-Tech asserts that the district court erred by failing to notify the parties in advance of its statutory construction of 21 U.S.C. § 321(ff)(1). Opening Br. 56-57. Federal Rule of Civil Procedure 56(f)(2) allows the district court to grant a summary judgment motion "on grounds not raised by a party" "[a]fter giving notice and a

reasonable time to respond." Here, the parties moved for summary judgment on the issue of whether DMAA was a constituent of a botanical, and the district court granted summary judgment on that issue, although it reached its conclusion by way of statutory construction, rather than determining whether DMAA had in fact been detected in geraniums. Assuming the court's reasoning required prior notice under Rule 56(f)(2), any error in failing to provide prior notice was harmless and there was no need for further discovery in light of the court's statutory construction. *See Spring St. Partners-IV, LP v. Lam*, 730 F.3d 427, 435-36 (5th Cir. 2013).

Hi-Tech points to two abandoned patent applications that claimed to have discovered a process for extracting a DMAA solution from geraniums that would contain DMAA in concentrations as high as 3%. Opening Br. 54-56. Hi-Tech argues that, after the district court's ruling, it understood for the first time that it would need to develop this evidence. That argument misconstrues the parties' dispute at summary judgment and the record before the district court.

The parties' primary dispute at summary judgment was whether "DMAA is 'naturally produced by geranium plants.'" Opening Br. 55. Hi-Tech had every incentive to demonstrate at summary judgment that these patent applications were accurate and verifiable, because they would prove that geraniums produce DMAA in significant quantities. Hi-Tech's experts were aware of these patent applications and referred to them in their declarations. *See* Doc. 108-6 at 355 (Heuer Decl.) ("Two published U.S. method patents, US 2012/0225144 and 2012/0225142, also report

that DMAA has also been detected in multiple species of geranium (including the *Pelargonium* and *Geranium* genus) where it was found to be present in concentrations as high as 3% on the inventor's extract."); *id.* at 353, 370-71 (similar); Doc. 108-7 at 237 (Simone Decl.) (citing patent application US 2012/0225144). Hi-Tech even introduced one of the applications during its deposition of a government expert and attempted to elicit evidence that "the purpose of the patent was to describe a method of extracting 1,3-DMAA from Geranium plants." Doc. 108-8 at 45 (Brown Dep. 171:23-25).

But Hi-Tech never relied on these abandoned patent applications—or any data connected to them—to argue that they reliably demonstrated that geraniums produced DMAA. *See* Doc. 108-1 (Hi-Tech Mot. Summ. J.); Doc. 119 (Hi-Tech Resp. to U.S. Mot. Summ. J.); Doc. 128 (Hi-Tech Reply in Supp. of Summ. J.). Indeed, Hi-Tech's expert Dr. Heuer cited these patent applications in his declaration setting out his expert opinion, but he could not verify whether the process described in the patent applications could actually produce DMAA, Doc. 130 at 31 (Heuer Dep. 118:1-5), had not seen any laboratory results related to the applications, *id.* at 58 (Heuer Dep. 228:17-21), and had not attempted to contact the authors of the applications, *id.* (Heuer Dep. 229:4-19).

If Hi-Tech had believed that further discovery related to these patent applications would have been useful at all, it would have undertaken it and presented its evidence at summary judgment. Indeed, if Hi-Tech could have demonstrated that

DMAA has been extracted from geraniums at levels as high as 3%, Hi-Tech could have shown that DMAA existed in geraniums at levels that were significantly higher than had ever been previously reported. Yet Hi-Tech did not rely upon these patent applications in its summary judgment briefing and did not point to any evidence that corroborated their claims. Hi-Tech cannot now claim that any error by the district court unfairly prevented it from investigating this path further.[13]

* * *

If this Court were to disagree and instead conclude that dietary ingredients include chemicals that have been produced by plants but not extracted from them, then a remand to district court would be necessary. The district court would have to determine whether, at summary judgment, there is a genuine issue of material fact about whether geraniums actually produce DMAA. Hi-Tech asserts that the district court squarely held against the government on this point, and quotes the court as holding that "the Government 'failed to meet its burden of establishing'" that DMAA is not found in geraniums. Opening Br. 42 (quoting Doc. 140 at 7). The court's full

[13] Indeed, Jared Wheat—Hi-Tech's sole shareholder—testified that it Hi-Tech had attempted to extract usable amounts of DMAA from geraniums but could not do so. Doc. 108-8 at 337 (Wheat Dep. 68:22-69:6) (Hi-Tech has "worked on extracting [DMAA] from the plant and the oil. We also looked at a fermentation process by which we could cause more DMAA to be yielded from the plant, but pretty much all of those were just commercially unfeasible as far as financially, to bring a plant extract that was going to be yielding high amounts of DMAA. The fermentation process I believe we can one day get to work. The technology is getting better. But as of right now it's still not there.").

quotation, however, was not a definitive holding at summary judgment. Instead, the court stated: "Nonetheless, this Court would be inclined to find that the Government has failed to meet its burden of establishing that DMAA has not been found in geraniums. That, however, does not end the inquiry in this Court's opinion." Doc. 140 at 7. In context, the court stated in dictum that it would be inclined to deny the government's motion for summary judgment on this point, but it declined to make an express ruling. *See id.* at 8 (stating that "DMAA *might be* in geraniums") (emphasis added). Instead, the court resolved the case on other grounds. *See id.* at 8-9 (holding that "it is inconceivable" that Congress intended for the United States have the burden of refuting any dietary supplement manufacturer's claim that "miniscule amounts of [a] chemical [occur] in obscure plants so that [manufacturers] could declare the substance a dietary ingredient under the statute").

If this case were remanded, the district court would first have to decide whether there was a genuine issue of material fact on this question, given the many "reasons to doubt the veracity of the studies that detected DMAA in geraniums," Doc. 140 at 7, which Hi-Tech presents on appeal as factually conclusive, Opening Br. at 42-45. There was no evidence that geraniums have a biologically plausible mechanism for producing DMAA, which further raises the likelihood that any studies detecting DMAA were afflicted by contamination or methodological errors. *See supra* p.9. Geraniums containing DMAA may have absorbed it from contaminated fertilizers rather than producing it on their own. *Id.* Furthermore, geraniums watered

with trace concentrations of DMAA suffered severe adverse effects, which would not make sense if geraniums produced DMAA on their own. *Id.* At a minimum, it is likely that reasonable minds could differ on whether it had been proven that geraniums produce DMAA.

II. DMAA IS AN UNSAFE FOOD ADDITIVE AND IS NOT GENERALLY RECOGNIZED AS SAFE AMONG SCIENTIFIC EXPERTS

Because DMAA is not a dietary ingredient but is present in food (*i.e.*, dietary supplements), it is a food additive. 21 U.S.C. § 321(s). As a food additive, DMAA is deemed by statute to be unsafe because there is no regulation authorizing its use and it is not subject to an exemption from regulation. 21 U.S.C. §§ 321(s), 348(a). And because it is unsafe, any food containing DMAA is considered adulterated. 21 U.S.C. § 342(a)(2)(C)(i).

Hi-Tech argues that DMAA is not an unsafe food additive because DMAA is "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures * * * to be safe under the conditions of its intended use," 21 U.S.C. § 321(s), *i.e.*, it is generally recognized as safe by scientific experts. To successfully rebut Hi-Tech's argument, the United States "need only show the lack of the proper reputation * * * for safety of the food additive among the appropriate experts, or that what reputation there is, is not based on adequate studies." *United States v. Articles of Food & Drug Consisting of Coli-Trol 80, F4C-60 Feed Grade, Entrol-S Medicated, Entrol-P*, 518 F.2d 743,

746 (5th Cir. 1975) (*Articles of Food & Drug*).[14] Under that standard, DMAA is not generally recognized as safe.

To be generally recognized as safe, it must be "common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food" that DMAA is safe for use as intended. 21 C.F.R. § 170.30(a). In other words, it is not enough for Hi-Tech to argue that there is a lack of evidence that DMAA is dangerous. Instead, Hi-Tech must affirmatively demonstrate that DMAA "is generally recognized by experts as *safe* based on scientific evidence." *United States v. An Article of Food*, 752 F.2d 11, 15 (1st Cir. 1985). DMAA does not pass this test because there are conflicting scientific views regarding its safety and because, at a minimum, it has not been sufficiently studied to result in a general recognition of its safety by scientific experts.[15]

[14] Fifth Circuit decisions issued before October 1, 1981, are considered precedential in this Court. *Bonner v. City of Prichard*, 661 F.2d 1206, 1209 (11th Cir. 1981) (en banc).

[15] Alternatively, DMAA could be considered generally recognized as safe if Hi-Tech had shown that DMAA was a substance used in food before 1958 and was shown to be safe through "experience based on common use in food." 21 U.S.C. § 321(s). Although Hi-Tech asserts that DMAA is contained in geraniums and that geraniums have been "routinely consumed" for over a century (Opening Br. 13), Hi-Tech does not argue that DMAA is generally recognized as safe based on its common use in food.

A. Evidence of Risk

To begin with, a number of scientific studies note that DMAA may cause, or at least is correlated with, significant deleterious effects on people's health. Two studies indicate that DMAA "may cause increases in blood pressure and hemorrhagic stroke," while another study recommends that people with high blood pressure should avoid DMAA. Doc. 107-8 at 32-33 (citations omitted). Eleven other studies describe "adverse outcomes that occurred after the consumption of DMAA-containing products." *Id.* at 33. There is evidence that "DMAA inhibits the activity of important liver enzymes *in vitro*," and that this enzyme inhibition "may be exacerbated" when DMAA is consumed with other substances. *Id.* at 34. Additionally, DMAA's chemical structure is similar to amphetamines, and the scientific literature "suggests that DMAA and amphetamines have similar physiological actions in the human body," particularly when DMAA is consumed with caffeine or alcohol, or used during exercise. *Id.* at 34-35.

Following the deaths of several service members who had consumed DMAA, the Department of Defense commissioned a scientific panel to study the health effects of DMAA among its soldiers. That panel's report studied 1,789 male and female soldiers of varying ages, races, backgrounds, and health histories. Doc. 107-5 at 195-99. The report was unable to identify a direct relationship between consuming DMAA and experiencing an adverse medical event, but the study did find that soldiers who had experienced *multiple* adverse medical events were more likely (at a

statistically significant level) to have consumed DMAA over a prolonged period of time. *Id.* at 211; *see also supra* pp.5-6. Accordingly, the report called for "further rigorous study designs" to better understand "the magnitude of the association of DMAA with adverse medical events." Doc. 107-5 at 172; *see also id.* ("DMAA should be further studied to evaluate its safety."). And in the meantime, the report recommended that products containing DMAA not be sold on any military installations because "the evidence supports sufficient risk, even if very low, of another death or catastrophic illness of a Service member who has used DMAA-containing products, without any offsetting benefit." *Id.* at 172.

Based on these and other studies, Dr. Dennis Keefe—director of FDA's Center for Food Safety and Applied Nutrition, Office of Food Additive Safety and expert in plant cell biology, molecular biology, and food chemical risk management—concluded that DMAA was not generally recognized as safe by qualified experts. Doc. 107-8 at 1-2, 8-13.

B. Lack of General Recognition of DMAA's Safety

Hi-Tech argues that it ought to have survived summary judgment because its four experts opined that DMAA was safe at the doses Hi-Tech recommends. Opening Br. 59. Three of those experts, however, declined to offer an expert opinion that DMAA is generally recognized as safe by scientific experts. Doc 107-5 at 105 (Dr. Mitchell Elkind declining to offer an opinion); *id.* at 127 (Dr. Michael Lumpkin declining to offer an opinion); *id.* at 7 (Dr. Marvin Heuer stating his "personal feeling"

that DMAA was generally recognized as safe, but explaining that he had not "been asked to apply that and make the final decision"). The remainder of their expert opinions came with significant qualifications that undermine Hi-Tech's claim that DMAA is generally recognized as safe.

For example, a large portion of the U.S. populace either has hypertension (chronically elevated blood pressure) or prehypertension (increased blood pressure that may lead to hypertension). Doc. 119-1 at 36-37. Hi-Tech's expert Dr. Elkind agreed that DMAA elevates blood pressure, Doc. 108-6 at 215, but testified that he was not aware of any studies evaluating how DMAA affects people with hypertension or prehypertension, Doc. 107-5 at 108.

Dr. Elkind additionally observed that the lack of studies on DMAA limited the knowledge available to the scientific community. He agreed with the Department of Defense's conclusion that "[w]ithout further rigorous study designs developed to evaluate the safety of DMAA * * * the magnitude of the association of DMAA with adverse medical events is uncertain." Doc. 107-5 at 116. To Dr. Elkind's knowledge, no such studies had been conducted. *Id.* Nor have there been any studies to evaluate the health effects of DMAA on people over the age of 55. *Id.* at 109. The lack of such studies necessarily prevents scientific experts from reaching a general consensus on whether DMAA is strongly or weakly associated with adverse medical events, or whether DMAA is safe or unsafe for people over the age of 55.

Hi-Tech's other experts similarly qualified their opinions. Dr. Heuer did "not disagree" with the statement that "some individuals may be predisposed to severe health consequences after using DMAA." Doc. 107-5 at 18. And Dr. Elkind, Dr. Heuer, and Dr. Lumpkin were unable to speak about the long-term effects of consuming DMAA, because they were not aware of any studies analyzing long-term DMAA consumption. *Id.* at 8, 110, 126. That is a particular concern for DMAA, because the Department of Defense report found that the strongest correlation between DMAA and multiple adverse medical events was when a person had consumed DMAA over a prolonged period of time. *Id.* at 210-11. Indeed, because some health effects are only evident over a prolonged period of exposure, FDA's regulatory definition of "safe" provides that one should look to the "cumulative effect of [a] substance in the diet" to determine whether the substance is safe. 21 C.F.R. § 170.3(i)(2).

To be sure, some studies did not observe harmful effects from consuming DMAA. *See, e.g.,* Doc. 107-8 at 34 (discussing a study by Schilling et al. (2013)). These studies, however, suffer from methodological limitations that prevent their observations from being broadly extrapolated. For instance, the Schilling study observed eight men for 24 hours after they consumed 25 milligrams of DMAA. *Id.* Notably, this dosage was considerably lower than the 45-135 milligrams of DMAA that Hi-Tech recommends for daily consumption. Doc. 108-4 at 31; Doc. 108-8 at 114-15. The Schilling study included no women, the subjects were all young, and

there was no follow-up to determine any long-term effects of repeated consumption. Doc. 107-8 at 34. Other studies finding no adverse effects from DMAA suffer from similar limitations. These studies observed groups of 16 people or fewer, and those people were young, "generally described as 'exercised-trained,'" and had low blood pressure. *Id.* at 38. Other studies did not record the age, weight, or blood pressure of the people being observed. *Id.* at 39. And one of these studies even recommended that DMAA should not be used by people with hypertension or prehypertension—suggesting that it may not be safe for these people. *Id.* at 38-39.

Hi-Tech's remaining expert, Dr. Matthew Lee stated in his declaration that DMAA is "safe when used as directed," Doc. 108-8 at 116, but did not state whether DMAA is generally recognized as safe. At his deposition, Dr. Lee stated for the first time that he believed DMAA was generally recognized as safe by scientific experts, although he "d[id]n't know the specific requirements" for this standard. *Id.* at 165-66 (Lee Dep. 65:14-67:5).

C. The District Court Correctly Granted Summary Judgement to the United States

On that record, the district court correctly granted summary judgment to the United States, explaining that Hi-Tech had failed to establish a genuine factual issue about whether the scientific community of qualified experts generally recognized DMAA as safe. Doc. 140 at 12 ("Hi-Tech has failed to present sufficient evidence" that "there is a consensus among experts regarding DMAA's safety"). That

conclusion was supported by the many studies the United States identified, which discussed the potential health risks associated with DMAA and the methodological limitations of the studies that found no or limited risk. Even discounting the United States' evidence, the district court noted that "the scientific literature on DMAA presents insufficient data to conclude that DMAA is safe or that DMAA causes harm because the sample sizes are too small." *Id.* at 11 (quoting *Sparling v. Doyle*, 2015 WL 4528759, at *35 (W.D. Tex. July 27, 2015)).

The district court's conclusion is consistent with the First Circuit's analysis in *United States v. An Article of Food*, 752 F.2d 11 (1st Cir. 1985). There, the United States submitted two expert affidavits opining that potassium nitrate (also known as saltpeter) was not generally recognized as safe for use in beverages, while the claimant submitted an expert affidavit to the contrary. *Id.* at 13. The First Circuit noted several fundamental deficiencies with the claimant's expert opinion, *id.* at 15, and held that the government experts' opinions "were sufficient to demonstrate the existence of genuine dispute among qualified experts concerning the safe use of potassium nitrate in beverages," *id.* at 15 n.6. Accordingly, the First Circuit held that the government's evidence "was sufficient to preclude a finding of 'general recognition' of safe use." *Id.*

The Second Circuit has reached the same conclusion in the context of determining whether a drug product was generally recognized as safe. *Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 803 (2d Cir. 1980) ("[E]ither the unawareness

of the drug product by experts generally or a genuine dispute among qualified experts regarding a drug product's safety and effectiveness preclude its qualifying for exclusion as 'generally recognized.'"). FDA has reiterated these judicial holdings when it promulgated regulations defining when a food additive is generally recognized as safe by scientific experts. 81 Fed. Reg. 54,960, 54,977 (Aug. 17, 2016) ("Importantly, general recognition of safety does not exist if there is a genuine dispute among qualified experts that the use of a substance is safe."). The district court was in good company when it held that the dispute among the parties' experts in this case—coupled with the limitations of the scientific studies relied upon by Hi-Tech—precluded a finding that DMAA is generally recognized as safe by qualified experts in the scientific community.

Hi-Tech contends that the district court improperly granted deference to the United States' expert, Dr. Keefe, and that a single expert's opinion cannot be a basis for granting summary judgment on the issue of whether DMAA is generally recognized as safe. Opening Br. 63-64. To be clear, though, the district court explained that its conclusion was supported not just by the lack of scientific consensus, but by the inadequacy of the current scientific literature. Doc. 140 at 11 ("[T]he scientific literature on DMAA presents insufficient data."); *id.* at 12 ("[T]he sample sizes of" Hi-Tech's studies are "simply too small to provide any convincing evidence regarding the safety of DMAA"); *see also Articles of Food & Drug*, 518 F.2d at 746 (substance will not be generally recognized as safe its reputation for safety "is not

based on adequate studies"). Nor did Dr. Keefe's testimony amount to a "heckler's veto." Opening Br. 63. As explained in his report, Dr. Keefe surveyed the published and unpublished studies concerning DMAA, evaluated their results and their methodologies, and formed an expert opinion that there was an insufficient basis for DMAA to be generally recognized as safe by scientific experts. Doc. 107-8 at 28-45. That opinion was supported by the dozens of studies Dr. Keefe reviewed, and Hi-Tech gives no credible reason for doubting the merits of that opinion.

Hi-Tech relies on *Articles of Food & Drug*, 518 F.2d 743, to argue that summary judgment was inappropriate (Opening Br. 61-62), but that case offers further support for the district court's holding. In *Articles of Food & Drug*, the Fifth Circuit held that the challenged drugs and food additive were not generally recognized as safe. 518 F.2d at 747. In passing, the Court stated that it would not be enough "to show merely a conflict in the evidence of general recognition, for even properly conducted studies may produce disagreement." *Id.* at 746. And while "the trial court's opinion suggests that any conflict in expert testimony is sufficient to prove the lack of a general reputation for safety," the Fifth Circuit held that this broad statement was unnecessary to resolve the case at hand when the evidence overwhelming supported the United States. *Id.* at 747. *Articles of Food & Drug* thus states that if a claimant offers evidence that a substance is generally recognized as safe, the United States must respond with evidence to the contrary. But if the government's evidence is meager and shows merely a bare conflict in some of the evidence, that will be insufficient. *Id.*

at 746. Instead, as the First Circuit and Second Circuit have held, the United States should demonstrate that there is a "genuine dispute" about whether the substance is generally recognized as safe by scientific experts. *An Article of Food*, 752 F.2d at 15 n.6; *Premo Pharm. Labs.*, 629 F.2d at 803. *Articles of Food & Drug* is entirely consistent with that standard, which the United States satisfied here.

D. Hi-Tech's Remaining Arguments Are Mistaken

1. Hi-Tech contends that the issue is not whether DMAA is safe under all circumstances, but instead whether Hi-Tech presented sufficient evidence that DMAA is safe at the dosage Hi-Tech recommends: somewhere between 45 milligrams per day, Doc. 108-4 at 31, to 135 milligrams per day, Doc. 108-8 at 114-15. As previously explained, *supra* pp.38-39, the studies Hi-Tech relies upon have methodological limitations that prevent their observations from being broadly extrapolated. Even assuming these studies were valid, several of them do not correspond to the higher ends of Hi-Tech's recommended dosage. Instead, they analyze whether 25 milligrams of DMAA results in adverse health effects, Doc. 108-4 at 44, or whether 75 milligrams of DMAA does, *id.* at 48. Hi-Tech identified no evidence that its recommended levels of consumption are generally recognized as safe for prolonged periods, for people with hypertension, or for other potential risk factors, such as use during exercise. *See supra* pp.37-39. Thus, the district court was

correct to conclude that there was insufficient evidence that DMAA is generally recognized as safe when consumed even at Hi-Tech's recommended levels.

2. Hi-Tech also suggests that FDA should proceed through rulemaking and regulation to determine whether DMAA is generally recognized as safe. Opening Br. 63. But Hi-Tech does not suggest that the absence of such a regulatory proceeding bars the United States from bringing a judicial action like this one to seize and condemn the products containing DMAA. And the courts are perfectly capable of determining whether a food additive is unsafe in the course of such a condemnation proceeding. *See, e.g.*, *Articles of Food & Drug*, 518 F.2d at 747; *An Article of Food*, 752 F.2d at 15-16.

3. Hi-Tech also points to draft guidance that FDA has recently published to assist members of the public who are seeking FDA's opinion regarding whether use of their food additive meets the generally recognized as safe standard. Opening Br. 62-63. Hi-Tech implies that under this draft guidance, DMAA would likely be determined to be generally recognized as safe. *Id.* That implication is mistaken.

FDA's draft guidance explains that a substance is not generally recognized as safe where, as here, there is "a genuine dispute among qualified experts that the use of a substance is safe" or "a severe conflict among experts regarding the safety of the use of a substance." Food & Drug Admin., U.S. Dep't of Health & Human Servs., *Best Practices for Convening a GRAS Panel: Guidance for Industry* 21 (Nov. 2017 Draft), available at https://www.fda.gov/downloads/Food/GuidanceRegulation/

GuidanceDocuments/RegulatoryInformation/UCM584930.pdf. "Thus, when generally available data and information document a genuine dispute, or severe conflict, in the larger scientific community," the substance cannot be said to be generally recognized as safe. *Id.* Instead, more research is required to fill the "data gaps" regarding the substance's safety, *id.*, as the district court concluded here in holding that DMAA is not generally recognized as safe, Doc. 140 at 11-12.

CONCLUSION

The Court should affirm the district court's judgment in favor of the United States.

Respectfully submitted.

Of Counsel:

ROBERT P. CHARROW
General Counsel

REBECCA K. WOOD
Chief Counsel, Food and Drug Division

ANNAMARIE KEMPIC
Deputy Chief Counsel, Litigation

JOSHUA A. DAVENPORT
Associate Chief Counsel

U.S. Food and Drug Administration

CHAD A. READLER
Acting Assistant Attorney General

BYUNG J. PAK
United States Attorney

/s/ Daniel Aguilar
SCOTT R. McINTOSH
DANIEL AGUILAR
Attorneys, Appellate Staff
Civil Division, Room 7266
U.S. Department of Justice
950 Pennsylvania Ave., NW
Washington, DC 20530
(202) 514-5432

JANUARY 2018

CERTIFICATE OF COMPLIANCE WITH FEDERAL RULE OF APPELLATE PROCEDURE 32(A)

I hereby certify that this brief complies with the requirements of Federal Rule of Appellate Procedure 32(a)(5) and (6) because it has been prepared in 14-point Garamond, a proportionally spaced font.

I further certify that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 11,592 words, excluding the parts of the brief exempted under Rule 32(f), according to the count of Microsoft Word.

/s/ Daniel Aguilar
DANIEL AGUILAR

CERTIFICATE OF SERVICE

I hereby certify that on January 5, 2018, I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the Eleventh Circuit by using the appellate CM/ECF system. I further certify that I will cause seven paper copies of this brief to be filed with the Court by sending them via Federal Express on the filing date.

The participants in the case are registered CM/ECF users and service will be accomplished by the appellate CM/ECF system.

/s/ Daniel Aguilar
DANIEL AGUILAR

ADDENDUM

ADDENDUM TABLE OF CONTENTS

Page

21 U.S.C. § 321. Definitions; generally

* * *

(f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.

* * *

(s) The term "food additive" means 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 (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include—

(1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or

(2) a pesticide chemical; or

(3) a color additive; or

(4) any substance used in accordance with a sanction or approval granted prior to September 6, 1958, pursuant to this chapter, the Poultry Products Inspection Act [21 U.S.C.A. § 451 et seq.] or the Meat Inspection Act of March 4, 1907, as amended and extended [21 U.S.C.A. § 601 et seq.];

(5) a new animal drug; or

(6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.

* * *

(ff) The term "dietary supplement"—

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

(2) means a product that—

(A) (i) is intended for ingestion in a form described in section 350(c)(1)(B)(i) of this title; or

(ii) complies with section 350(c)(1)(B)(ii) of this title;

(B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and

(C) is labeled as a dietary supplement; and

(3) does—

(A) include an article that is approved as a new drug under section 355 of this title or licensed as a biologic under section 262 of Title 42 and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 342(f) of this title; and

(B) not include—

> > (i) an article that is approved as a new drug under section 355 of this title, certified as an antibiotic under section 357 of this title, or licensed as a biologic under section 262 of Title 42, or
>
> > (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,
>
> which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.

Except for purposes of paragraph (g) and section 350f of this title, a dietary supplement shall be deemed to be a food within the meaning of this chapter.

21 U.S.C. § 331. Prohibited acts

The following acts and the causing thereof are prohibited:

> (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.
> (b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.
>
> (c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

21 U.S.C. § 334. Seizure

(a) Grounds and jurisdiction

> (1) Any article of food, drug, or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which

may not, under the provisions of section 331(*ll*), 344, or 355 of this title, be introduced into interstate commerce, shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which the article is found. No libel for condemnation shall be instituted under this chapter, for any alleged misbranding if there is pending in any court a libel for condemnation proceeding under this chapter based upon the same alleged misbranding, and not more than one such proceeding shall be instituted if no such proceeding is so pending, except that such limitations shall not apply (A) when such misbranding has been the basis of a prior judgment in favor of the United States, in a criminal, injunction, or libel for condemnation proceeding under this chapter, or (B) when the Secretary has probable cause to believe from facts found, without hearing, by him or any officer or employee of the Department that the misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading to the injury or damage of the purchaser or consumer. In any case where the number of libel for condemnation proceedings is limited as above provided the proceeding pending or instituted shall, on application of the claimant, seasonably made, be removed for trial to any district agreed upon by stipulation between the parties, or, in case of failure to so stipulate within a reasonable time, the claimant may apply to the court of the district in which the seizure has been made, and such court (after giving the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business, to which the case shall be removed for trial.

21 U.S.C. § 342. Adulterated food

A food shall be deemed to be adulterated—

(a) Poisonous, insanitary, etc., ingredients

(1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health.

(2) (A) if it bears or contains any added poisonous or added deleterious substance (other than a substance that is a pesticide chemical residue in or on a raw agricultural commodity or processed food, a food additive, a color additive, or a new animal drug) that is unsafe within the meaning of section 346 of this title; or

(B) if it bears or contains a pesticide chemical residue that is unsafe within the meaning of section 346a(a) of this title; or

(C) if it is or if it bears or contains

(i) any food additive that is unsafe within the meaning of section 348 of this title; or

(ii) a new animal drug (or conversion product thereof) that is unsafe within the meaning of section 360b of this title; or

(3) if it consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food; or

(4) if it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health; or
(5) if it is, in whole or in part, the product of a diseased animal or of an animal which has died otherwise than by slaughter; or

(6) if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or

(7) if it has been intentionally subjected to radiation, unless the use of the radiation was in conformity with a regulation or exemption in effect pursuant to section 348 of this title.

21 U.S.C. § 348. Food additives

(a) Unsafe food additives; exception for conformity with exemption or regulation

A food additive shall, with respect to any particular use or intended use of such additives, be deemed to be unsafe for the purposes of the application of clause (2)(C) of section 342(a) of this title, unless—

> (1) it and its use or intended use conform to the terms of an exemption which is in effect pursuant to subsection (j) of this section;
>
> (2) there is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used; or
>
> (3) in the case of a food additive as defined in this chapter that is a food contact substance, there is—
>
> > (A) in effect, and such substance and the use of such substance are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used; or
> >
> > (B) a notification submitted under subsection (h) of this section that is effective.

While such a regulation relating to a food additive, or such a notification under subsection (h)(1) of this section relating to a food additive that is a food contact substance, is in effect, and has not been revoked pursuant to subsection (i) of this section, a food shall not, by reason of bearing or containing such a food additive in accordance with the regulation or notification, be considered adulterated under section 342(a)(1) of this title.