No. 17-13376-K

IN THE UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

HI-TECH PHARMACEUTICALS, INC., *ET AL.*,
***Appellants*,**
v.
UNITED STATES OF AMERICA,
***Appellee*.**

On appeal from the United States District Court for the Northern District of Georgia, No. 1:13-cv-03675-WBH

REPLY BRIEF FOR APPELLANTS HI-TECH PHARMACEUTICALS, INC. & JARED WHEAT

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CERTIFICATE OF INTERESTED PERSONS

The following is a list of all **additional** known judges, attorneys, persons, associations of persons, firms, partnerships, corporations, and other legal entities that have an interest in the outcome of this case, including subsidiaries, conglomerates, affiliates and parent corporations, any publicly held company that owns 10 percent or more of a party's stock, and other identifiable legal entities related to a party:

[**no new parties**]

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ARGUMENT

Concerns about agency overreach are at the heart of this case, and on appeal the FDA has made the problem worse. "A fundamental principle in our legal system is that laws which regulate persons or entities must give fair notice of conduct that is forbidden." *F.C.C. v. Fox Television Stations*, 567 U.S. 239, 253 (2012). Yet the Government has found itself so unsure of how even *it* believes DSHEA's language should apply to DMAA that it has changed its position on the matter no fewer than three times during this litigation. It cited one interpretation of DSHEA beforehand, when it forced other companies to stop marketing DMAA. *See* Hi-Tech Br. 26. Then it asserted a different one when it seized Hi-Tech's supplements. *See id.* at 27-28. It offered yet another when it asked the District Court for summary judgment. *See id.* at 29. Now it says still another interpretation—the District Court's *sua sponte* one, which has so little support in DSHEA's text that the Government previously failed to discern it—is "correct[]." U.S. Br. 15. This new interpretation is so correct, the Government declares, that it warranted summary judgment without prior notice to Hi-Tech and Wheat or an opportunity to show that DMAA is marketable under it.

That is not how federal regulation of any industry, much less a multi-billion-dollar one, is supposed to work. Agencies are supposed to announce their interpretations of the statutes they administer before they seize private property—not afterwards, and certainly not for the first time in response briefs on appeal. Agencies are supposed to justify their actions by citing the text's ordinary meaning—not canons of interpretation that effectively ask the courts to write new words into the U.S. Code. When agencies seize private property based on their interpretations of those statutes, due process is supposed to demand both "notice" to affected persons and an "opportunity to be heard." *United States v. James Daniel Good Real Prop.*, 510 U.S. 43, 48 (1993) (citing *Fuentes v. Shevin*, 407 U.S. 67, 82 (1972)). The Government's positions on both questions presented are antithetical to these principles.

I. The District Court erred in holding that DMAA is not a freely marketable "dietary ingredient"

An overarching point about the Government's position on the first question presented bears emphasis at the outset. In now contending that "constituent" in 21 U.S.C. § 321(ff)(1)(F) "must" connote something more limited than its ordinary meaning, the Government glosses over

what is really at stake. U.S. Br. 19. DSHEA gives the FDA authority to stop companies from distributing even "dietary ingredients," as that term is defined under § 321(ff)(1), so long as it can affirmatively show they "present[] a significant or unreasonable risk of illness or injury." 21 U.S.C. § 342(f)(1)(A). So the Government is asking the Court to narrow § 321(ff)(1) not because the FDA wants to retain power to ban dietary ingredients that are "unsafe," U.S. Br. 15, but because it wants the power to ban ingredients, like DMAA products, for which it cannot make that showing at all.

That request flouts the letter and spirit of DSHEA. It is not mere happenstance that DSHEA's language is as broad as it is. As the Third Circuit has observed, "Congress passed DSHEA after a long-running dispute with the FDA about how strictly dietary supplements should be regulated." *NVE, Inc. v. Dep't of Health & Human Servs.*, 436 F.3d 182, 186 (3d Cir. 2006). The Senate Report said the DSHEA amendments would stop the FDA from continuing to "treat dietary supplements as 'food additives'" and thereby "shift[ing] to the manufacturer the burden of establishing the supplement's safety." S. Comm. on Labor and Human Res., Dietary Supplement Health and Education Act of 1994, S.

Rep. 103-410, at 21 (1994).[1] In effectuating that result, Congress broadly defined the "dietary ingredients" that would be presumptively marketable, including all "constituent[s]" of not only "vitamin[s]," "mineral[s]," "amino acid[s]," and "herb[s] or other botanical[s]," but also "dietary substance[s] for use by man to supplement the diet by increasing the total dietary intake." 21 U.S.C. § 321(ff)(1)(A)-(F).

So the Government is wrong to suggest that it would "undercut the framework that Congress established" if courts interpreted "constituent" in accordance with its ordinary meaning. U.S. Br. 23. The framework Congress established makes "an almost limitless variety of ingredients" presumptively marketable. Scott Bass & Emily Marden, *The*

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[1] As the Third Circuit also has noted, "DSHEA's chief sponsors stated their intent that a" truncated "Statement of Agreement" placed in the Congressional Record "would comprise the entire legislative history for DSHEA and that 'no other reports or statement be considered as legislative history for the bill'"—including, presumably, the Senate Report. *NVE*, 436 F.3d at 193 n.4 (quoting 140 Cong. Rec. H11173, 11179 (1994); 140 Cong. Rec. S14798, 14801 (1994)). The Third Circuit rightly called this disclaimer's effect "debatable," and courts have not consistently applied it. *Id.* (collecting cases). Regardless, whether or not the Senate Report counts as formal "legislative history" in light of the Statement of Agreement, it stands as evidence of the background against which Congress adopted DSHEA's broad definition of "dietary ingredient." *Cf. id.* (noting that the Third Circuit would "assume that, despite the Statement of Agreement, previous drafts of DSHEA are indicative of congressional intent").

New Dietary Ingredient Safety Provision of DSHEA: A Return to Congressional Intent, 31 AM. J.L. & MED. 285, 296 (2005) (hereinafter "Bass & Marden"). It presumes that the FDA will fulfill its responsibilities not by asking courts to limit the universe of presumptively safe dietary ingredients, but by establishing which specific ingredients are unsafe. *See* 21 U.S.C. § 342(f). Insofar as the Government's position would effectively relieve it of that burden, it is that position, not Hi-Tech and Wheat's, that would undercut the statutory framework.

A. The Government failed to satisfy its burden of establishing that DMAA does not naturally occur in geraniums

With those realities in mind, the interpretive questions at hand are neither difficult nor close. The Government now appears to confess error on the arguments it made at the summary-judgment stage. When the Government moved for summary judgment, it stated that the dispositive question was: "is DMAA naturally produced by geranium plants?" Doc. 107-1 at p. 1. The Government argued that it was entitled to summary judgment because the undisputed evidence established that geranium plants do not naturally produce DMAA. But the District Court did not adopt that argument, and the Government does not ask

this Court to adopt it as an alternative ground for affirming the judgment below. Instead, the Government maintains that if this Court rejects the new interpretation of DSHEA the District Court adopted *sua sponte*, "a remand" is "necessary" so the District Court may assess whether, under the interpretation of DSHEA the parties advanced below, "there is a genuine issue of material fact about whether geraniums actually produce DMAA." U.S. Br. 31.

To the extent the Government is acknowledging that the record did not support the arguments it made for summary judgment, it is correct. But to the extent the Government is asserting that a remand is needed if this Court rejects the District Court's narrowing of the statute, the Government is ignoring the burden of proof it bore on this issue. It was not Hi-Tech and Wheat's burden, as the Government now suggests, to "prove" that DMAA is a "dietary ingredient" by establishing "that geraniums produce DMAA." *Id.* at 33. As the District Court ruled and the Government conceded below, it had the burden, as the party seeking forfeiture, to "establish[] that DMAA has *not* been found in geraniums." Doc. 140 at p. 7 (emphasis added).

The Government still has not identified evidence satisfying that

burden. It does not deny that it has abandoned the Mississippi and Texas studies, which failed to report that they had detected DMAA in geraniums. *See* Hi-Tech Br. 20-23. The other considerations to which the Government points are not substantial evidence that DMAA does not naturally occur in the plants. *See* U.S. Br. 32-33. They are but criticisms of certain evidence Hi-Tech offered, in its own defense, to establish the contrary proposition. The Government complains that "[t]here was no evidence that geraniums have a biologically plausible mechanism for producing DMAA." *Id.* at 32. It asserts that the plants "may have absorbed [DMAA] from contaminated fertilizers." *Id.* It cites testimony from the author of a study relied upon by Hi-Tech and Wheat that when he watered geraniums "with trace concentrations of DMAA," they "suffered severe adverse effects." *Id.* at pp. 32-33. As Hi-Tech and Wheat's opening brief explains, those criticisms are not well-founded for various reasons. *See* Hi-Tech Br. 28-29.[2] But the overarching point is

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[2] The District Court rightly drew no inference from the anecdote in which one study's author watered geraniums with DMAA. The Government cites no testimony concerning what conclusion a court should draw from that testimony, and none is apparent. As Hi-Tech and Wheat have explained in discussing the GRAS issue, "[t]oo much of anything—

that none affirmatively establishes that DMAA does *not* naturally occur in geraniums.

The upshot is that a remand is not needed. Once the Government cast aside the Mississippi and Texas studies, it was left with no substantial evidence that DMAA does not naturally occur in geraniums. *See* Hi-Tech Br. 27-29, 43-44. Under the proper interpretation of § 321(ff)(1), the record before the District Court compelled summary judgment for Hi-Tech and Wheat.

B. The Government does not persuasively defend the District Court's *sua sponte* interpretation

Unable to defend the arguments it made below, the Government pivots on appeal. Its response brief changes the United States' position, embraces the District Court's interpretation, and maintains that "[t]o be a dietary ingredient, DMAA 'must have been extracted from a plant or plant-like organism'" in non-"trace" amounts. U.S. Br. 14, 20 (quoting Doc. 140 at p. 8).

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coffee, sugar, even water—can be dangerous or even deadly." Hi-Tech Br. 58.

The Government's change of tune, at this juncture of this forfeiture action, deepens the APA and constitutional problems the case already presented. *See* Hi-Tech Br. 52-54.[3] If the FDA had issued warning letters announcing this interpretation, manufacturers could have conformed their conduct to that interpretation. As the Government acknowledges, Wheat testified that he believes the industry can "one day" develop a "'fermentation process by which we could cause more DMAA to be yielded from the plant.'" U.S. Br. 31 n.13 (quoting Doc. 108-8 at p. 337, tr. 68:22-69:6). That day might have come sooner had the FDA acted differently. By the time the Government adopted its interpretation *du jour*, it was too late for companies to adjust.

Altering the ground rules in this manner—after-the-fact, after-the-seizure, even after-the-appeal—would be problematic even when unambiguous statutory language required an agency to go that route. But it is especially troubling in light of what the statute at issue says

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[3] As the Government observes, Hi-Tech and Wheat's references to 42 U.S.C. § 1983 in their opening brief as a shorthand for the constitutional issues implicated by the FDA's actions is inapt. The officials responsible for this seizure and forfeiture action work for the federal government. So the constitutional issues do not implicate § 1983 itself, but rather, as Hi-Tech's APA complaint alleged, the Fifth Amendment's Due Process Clause more generally. *See, e.g.*, Doc. 41 at ¶¶ 50-53.

about the matter at hand. As the Government's own arguments reveal, far from being compelled or even suggested by DSHEA, the Government's new interpretation is refuted by it.

1. The District Court's interpretation is wrong

Perhaps most important, the dictionary definitions the Government cites as evidence of "ordinary meaning" only confirm that "constituent" means no more and no less than a component of a larger whole. U.S. Br. 15 (quoting *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 134 S. Ct. 1749, 1756 (2014)). *Merriam-Webster's* defines "constituent" as "an essential part," observing that the word connotes a "formative" character. *See* U.S. Br. 16 (citing MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY 248 (10th ed. 1998) (hereinafter "MERRIAM-WEBSTER'S"). The same dictionary defines the synonym "element" in equally broad terms, calling it "one of the parts of a compound or complex whole." *Id.* at 17 (quoting MERRIAM-WEBSTER'S, *supra*, at 373).

Those definitions make the outcome here straightforward. They do not suggest that a constituent's "essential and formative character" turns on whether people have extracted usable quantities of it in the past. MERRIAM-WEBSTER'S, *supra*, at 373. Its "essential and formative

character" turns only on whether it is "part" of the plant's "complex whole." *Id.* That is the way this word is used in ordinary parlance of scientists and non-scientists alike. *Cf.* TIMOTHY PAUL SMITH, HIDDEN WORLDS: HUNTING FOR QUARKS IN ORDINARY MATTER 51 (Princeton Univ. Press 2003) (calling quarks "the basic constituents of matter" even though science has "never isolated a quark" and perhaps "never will"). The fact that companies previously have extracted a compound from a plant may serve as evidence that it is, in fact, in the plant. But the fact that a compound detected in a plant has not been extracted in the past does not mean that it is not, in ordinary parlance, one of the plant's "constituents." In asserting otherwise, the Government is ignoring the principle, emphasized in the treatise it invokes, that general words "are to be accorded their full and fair scope" and "not to be arbitrarily limited." ANTONIN SCALIA & BRYAN A. GARNER, READING LAW 101 (2012) (hereinafter "READING LAW").

That treatise also stresses "avoid[ing] a reading" that "renders some words altogether redundant," *id.* at 176, and the Government does not deny that its reading would have that effect on § 321(ff)(1)(F)'s inclusion of "extract[s]" on the dietary-ingredient list, *see* Hi-Tech Br. 47-

48. The Government cannot flip this canon in its favor by asserting that the ordinary meaning of "constituent" would inject even more redundancies into the list. *See* U.S. Br. 21. By the Government's own definitions, the three items it claims would be "superfluous"—concentrates, metabolites, and extracts—are not component parts of the plants themselves. A "concentrate" is a mixture in which the plant's parts are more "concentrated" than they are in the plant. *Id.* at 18-19 n.7. A "metabolite" is a "product" of the plant's "metabolism," produced after it ingests outside substances. *Id.* at 19 n.10. An "extract" is not the components as they appear in the plant, but a "product" prepared "by extracting" them. *Id.* at 19 n.8. Each item has independent significance, and by listing each, § 321(ff)(1)(F) underscores that "the *broadest possible* range of dietary ingredients" is presumptively marketable. Bass & Marden, *supra*, at 295. Particularly by listing both "extract[s]" and "constituent[s]," the statute encompasses not only "extract[ed]" plant parts, but also unextracted parts companies replicate through synthesis or other processes.

The Government thus has things backwards when it argues that § 321(ff)(1)(F)'s list actually *limits* the meaning of "constituent," to "'a subset of all the things or actions that it covers.'" U.S. Br. 18 (quoting

READING LAW, *supra*, at 196). The canon the Government is invoking to make that argument, *noscitur a sociis*, is a poor fit here. The Government's relied-on treatise explains that this canon counsels reading an ordinarily general term in a limited sense only if, in the context of the statute and list in which the term appears, that limited sense is the term's "ordinary meaning." READING LAW, *supra*, at 196. So in one decision the Government cites, the Minnesota Court of Appeals held that the word "case" in a list in a firearms statute had the "specific technical meaning" it has "in relation to firearms," not the more general meaning it has outside that context. *State v. Taylor*, 594 N.W.2d 533, 535 (Minn. Ct. App. 1999). But the Government has not pointed to any evidence, other than perhaps the FDA's own arbitrary attempts to limit the statute,[4] of someone using "constituent" in ordinary parlance in a way that

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[4] The only instance the Government has cited in which someone used the term in a way it advocates here is from the FDA itself, in never-finalized draft guidance relating to the FDCA's New Dietary Ingredient provisions. *See* U.S. Br. 17 (citing FDA, *Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* 76 (Draft July 2011) (hereinafter "NDI Draft Guidance")). That document "[c]ontains [n]onbinding [r]ecommendations," is [n]ot for [i]mplementation," and does not operate to bind FDA or the public." NDI Draft Guidance, *supra*, at 1, 9. Courts do not "accord either *Chevron* deference or the lesser deference applicable to interpretative rules"

limits it to parts with histories of extraction.

Nor has the Government pointed to anything in DSHEA's statutory history or context suggesting that Congress had that limiting principle in mind. The Government is wrong when it speculates that the statute draws the relevant line between presumptively safe "dietary ingredients" and presumptively unsafe "food additives" based on whether "people already consumed" them. U.S. Br. 23. Numerous items qualify as "dietary ingredients" whether or not someone has eaten them in the past. *See* 21 U.S.C. § 350b(a)(2) (regulating "new" dietary ingredients). And because other provisions like § 342(f) let the FDA ban ingredients that are unsafe, § 321(ff)(1) "is *not* a safety provision." Bass & Marden, *supra*, at 295. Regardless, the Government is wrong to suggest that a constituent that lacks a history of extraction necessarily lacks a history of being consumed. Whether or not DMAA has a history of being extracted, the record shows that people have consumed geraniums for "over 100 years." Hi-Tech Br. 13 (quoting Doc. 108-6 at p. 352, ¶53). People thus have been consuming DMAA.

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to agency policies in "draft form" of this sort. *S. Utah Wilderness Alliance v. Dabney*, 222 F.3d 819, 829 (10th Cir. 2000); *accord Greenfield v. Yucatan Foods, L.P.*, 18 F. Supp. 3d 1371, 1374 (S.D. Fla. 2014).

The Government's attempts to cabin the consequences of its interpretation only reinforce how little sense it makes. The Government does not deny that practical considerations have led manufacturers to synthesize resveratrol and pterostilbene, familiar components of grapes and blueberries that serve as health-promoting antioxidants. *See id.* at 49. But the Government suggests that these ingredients would count as "constituents" under its interpretation because "there are scientific studies that indicate these chemicals actually have been derived from plants" at higher levels than those "at which DMAA has been detected in geraniums." U.S. Br. 25-26. The articles the Government cites refer to extractions of these compounds not from grapes and blueberries, but knotweed and kino trees. *See id.* at 25. So the Government's interpretation would view these compounds as "constituents" of the weed and tree, not the fruits. It would deem them "constituents" only after science developed an extraction process, not before. And it would deem them "constituents" only because they happen to be present at levels above some threshold level the Government currently is unwilling to specify.

That interpretation of DSHEA is the one that "does not make sense." *Id.* at 26. The Government may be right when it says that at-

tributing "constituent" its ordinary meaning will make it more difficult for the FDA to ban dietary supplements on the theory that their components are not dietary ingredients. But that is the system Congress put in place. When the FDA wants to ban supplements, it should focus on the principal role Congress envisioned for it, using rulemakings to show that certain supplements are unsafe. In the relatively few cases in which the FDA will have grounds for banning supplements solely because their ingredients are not constituents of botanicals, the FDA must do what it could not do here: it must offer the courts reliable evidence showing that the substance is not a naturally occurring part of a plant. It can avoid bringing meritless cases like this one by more carefully choosing the evidence it relies on and eschewing flawed studies like those that USADA commissioned from the University of Mississippi. Either way, the FDA can perform its functions without asking the courts to write limitations into the statute that are not there.

2. The District Court should have allowed Hi-Tech and Wheat to develop the record relating to the new interpretation

At the very least the Government has not adequately defended the District Court's decision not to allow discovery on the issues its *sua*

sponte interpretation raised. The Government offers no reason why, once the District Court determined that the dispositive issues were different from the ones under which the Government had prosecuted this action, the Court should not have allowed the parties to create a record that addressed those issues.

The Government misses the point when it criticizes Hi-Tech and Wheat for not further "develop[ing]," before the District Court announced its interpretation, the limited evidence in the record that happened to address these issues. In light of the premises on which the parties were litigating, "further discovery" related to the two patent applications referenced in Hi-Tech and Wheat's expert declarations was not a pressing matter. U.S. Br. 29. Hi-Tech and Wheat had introduced numerous studies finding that DMAA is present in geraniums. *See* Hi-Tech Br. 41-43. They also had shown that the studies on which the Government premised the seizure were seriously flawed. *See id.* at 18-23. The patent applications were a much less significant piece of the puzzle at that time.

Things would have been different if Hi-Tech and Wheat had been aware of the issues the District Court eventually would deem disposi-

tive. To be clear, the problem here is not simply the possibility of the patent applications standing as substantial evidence that Hi-Tech and Wheat could prevail under the District Court's interpretation. The more fundamental concern is that the lack of notice about what issues were dispositive led to a seizure and forfeiture without a full vetting of all relevant considerations and full discovery on the issues. The due-process principles that should have prompted the Government to dismiss this case when it abandoned the Mississippi and Texas studies also should have prompted the District Court to give Hi-Tech and Wheat notice and an opportunity to be heard.

II. The District Court erred in holding that DMAA is not "Generally Recognized as Safe"

The Government also has failed to adequately defend the District Court's entry of summary judgment on Hi-Tech and Wheat's alternative argument that DMAA is marketable because it is generally recognized as safe. *See* Hi-Tech Br. 57-65. The Government nit-picks at the methodologies of some studies Hi-Tech and Wheat's experts relied upon and cherry-picks language from others. That approach is inconsistent with "the fundamental principle that at the summary judgment stage, rea-

sonable inferences should be drawn in favor of the nonmoving party." *Tolan v. Cotton*, 134 S. Ct. 1861, 1868 (2014). At the very least this testimony created questions of fact warranting a trial.

A. Hi-Tech offered substantial evidence that DMAA is generally recognized as safe

The Government understates the value of the expert testimony Hi-Tech and Wheat offered below. Four experts testified that DMAA is safe at the doses recommended by Hi-Tech, and two specifically opined that the scientific community generally recognizes DMAA to be safe at those doses.

The Government is wrong when it asserts that one of those two witnesses, Dr. Heuer, actually "declined to offer an expert opinion that DMAA is generally recognized as safe by scientific experts." U.S. Br. 36. Heuer stated in his declaration that "[i]n my opinion this product would be eligible for a Generally Recognized As Safe (GRAS) determination." Doc. 108-6 at p. 359, ¶63. In the portions of his deposition the Government characterizes as a disclaimer of an opinion on this issue, he simply testified that because Hi-Tech viewed DMAA as a dietary ingredient for which no GRAS determination was needed, he had not "been asked to

apply that and make the final decision." U.S. Br. 36-37 (quoting Doc. 107-5 at 7). He opined no fewer than four times during that deposition that DMAA would qualify as GRAS if it were not a dietary ingredient. *See* Doc. 130 at p. 17, tr. 63:10-17 & 64:1-2; *id.* at p. 20, tr. 74:6-16; *id.* at p. 25, tr. 94:10-13.

The Government likewise is wrong when it claims that another defense expert, Dr. Lee, did not actually opine that DMAA is GRAS. Lee testified that DMAA is "generally recognized as safe at recommended doses." Doc. 108-8 at p. 190, tr. 162:22-163:14. The Government protests that Lee "d[id]n't know the specific [GRAS] requirements" at his deposition. U.S. Br. 39. But his inability to regurgitate language from the Code of Federal Regulations during a deposition does not change his repeated testimony that DMAA is considered safe. *See* Doc. 108-8 at p. 165, tr. 65:8-18; *id.* at p. 185, tr. 145:4-10; *id.* at p. 196, tr. 189:13-15.

Although the Government maintains that a "lack of studies" rendered this testimony insufficient, ample evidence supports their conclusions. Over the last 10 years, researchers measured DMAA's effects on over 160 men and women, for periods of up to 12 weeks, at varying dosage levels and under diverse environmental conditions. *See* Doc. 108-4

at pp. 42-55, ¶¶32-56; Doc. 108-6 at pp. 215-24, ¶¶52-73; Doc. 108-8 at pp. 116-22, ¶¶60-75; Doc. 108-6 at pp. 361-63, ¶¶68-70. The researchers collected data on heart rate, blood pressure, body temperature, and other health indicators. The results, which were published and peer-reviewed, consistently concluded that taking DMAA at the dosages recommended by Hi-Tech's labels produces only "modest" (Doc. 108-6 at p. 348, ¶46), "transient" (Doc. 108-4 at p. 48, ¶43), and "statistically insignificant" increases in blood pressure that have "no meaningful effect" (Doc. 108-8 at p. 119, ¶66). Recent animal studies display similar results, and indicate that adverse effects only begin occurring at dosages much higher than Hi-Tech recommends. *See* Doc. 108-4 at pp. 45-47, ¶¶38-42; Doc. 108-6 at pp. 222-24, ¶¶69-73; *id.* at pp. 361-63, ¶¶68-70.

The Government's brief selectively quotes from some of these studies in an attempt to suggest that DMAA might not be safe after all. For example, the Government observes that one study "indicates that DMAA 'may cause increases in blood pressure,'" and that another "recommends that people with high blood pressure should avoid DMAA." U.S. Br. 35 (citations omitted). But causing minimal and temporary increases in blood pressure does not make DMAA unsafe. The same could

be said of caffeine and countless other ingredients on the market today. *See, e.g.*, Shelden D. Sheps, Mayo Clinic, *Caffeine: How does it affect blood pressure?* https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/expert-answers/blood-pressure/faq-20058543 (last visited Jan. 24, 2018). Moreover, the two studies at issue dispel the Government's aspersions. One concluded that there was no meaningful impact on blood pressure when DMAA was consumed at recommended dosages. *See* Doc. 108-4 at pp. 48 & 74-77, ¶¶44 & 94 (summarizing Bloomer 2011a study). The other concluded that, after 14 days of consuming DMAA-containing supplements, people experienced "no significant differences" in heart rate or blood pressure. *Id.* at pp. 50-51, ¶¶47-48 (summarizing Farney 2012 study).

The Government has no basis for attacking the breadth of these studies. It says that their durations are too short, that the subjects are too few, and that none evaluates DMAA's potential long-term effects. *See* U.S. Br. 37-39. Those criticisms cannot support the entry of summary judgment on this issue. The Government's own expert conceded that there is no "minimum number of subjects" or "minimum required duration of such a study that's required." Doc. 108-6 at p. 19, tr. 45:10-

15. Moreover, the record contains evidence of DMAA's long-term effects. One of Hi-Tech and Wheat's experts testified that "studies that showed transient effects on blood pressure are not expected to have long-term adverse consequences on cardiac health." Doc. 108-8 at pp. 53-54, ¶53. Another expert testified that "[t]here is no evidence that longer-term use of DMAA (up to 10 weeks) causes a chronic elevation in blood pressure." Doc. 108-6 at p. 216, ¶53.

The Government also cannot defend the District Court's entry of summary judgment on the theory that researchers in those studies administered DMAA at dosage levels that were too low. In particular, the Government singles out one study that administered 25 milligrams of DMAA. *See* U.S. Br. 38-39. But one of Hi-Tech's experts testified that "[t]he dosage of DMAA recommended for performance enhancement is approximately 25 mg per serving." Doc. 108-6 at p. 212, ¶44. And while Hi-Tech recommends a dose of higher than 25 milligrams in some products, the Government's brief does not address the many studies in which researchers administered more than 25 milligrams without meaningful adverse effects. *See, e.g.*, Doc. 108-4 at p. 48, ¶44 (50 or 75 mg); *id.* at pp. 52-53, ¶52 (50 mg DMAA plus 250 mg caffeine); *id.* at p.

54, ¶55 (twice the maximum recommended amount of DMAA); *id.* at pp. 54-55, ¶56 (50, 75, or 100 mg).

Ultimately, the Government is complaining that there isn't a study accounting for *all* possible effects on *each* segment of the population—on people over 55, or people with prehypertension or hypertension, or people who exercise. *See* U.S. Br. 37. But the law does not require any such showing. A manufacturer must establish a "reasonable certainty," not an absolute one, that "the substance is not harmful under the conditions of its intended use." 21 C.F.R. § 170.3(i). As one of Hi-Tech's experts explained, "to study DMAA under all environmental conditions, with all combinations of co-morbidities and all potential drug interactions, is impossible and unrealistic." Doc. 108-8 at pp. 122-23, ¶76. The Government's expert admitted that the law imposes no requirement that studies be performed on a particular demographic or subset of people. *See* Doc. 108-6 at p. 30, tr. 88:14-18. Hi-Tech and Wheat's four expert declarations, and the many clinical studies they relied on, at least gave rise to a factual dispute on whether the scientific community generally recognizes DMAA as safe.

B. The Government's GRAS evidence could not compel summary judgment

On the other hand, the Government overstates the value of the limited expert testimony it offered on this issue. Hi-Tech and Wheat's witnesses relied heavily on studies involving experimental design, which one of them testified is "[t]he strongest study design in clinical research." Doc. 108-6 at p. 228, ¶81. The Government's sole expert based his opinion largely on weaker forms of research. The Government emphasizes his claim that "[e]leven other studies describe 'adverse outcomes that occurred after the consumption of DMAA-containing products.'" Doc. 140 at p. 11; U.S. Br. 35 (quoting Doc. 107-8 at ¶24). But those "studies" are more accurately described as "case reports," which are post-hoc analyses of adverse events suffered by particular people who consumed DMAA. It is widely accepted among scientists that case reports have the "least reliable" value in deducing scientific cause and effect of a particular substance on humans. Doc. 108-6 at p. 224, ¶75. Courts have deemed their findings "unreliable" and "unacceptable." *See, e.g.*, *Sparling v. Doyle*, No. EP-13-CV-323-DCG, 2015 WL 4528759, at *25 (W.D. Tex. July 27, 2015); *United States v. 50 Boxes . . . Cafergot P-B Suppositories*, 721 F. Supp. 1462, 1465 (D. Mass. 1989).

The FDA knows the pitfalls of case reports. In 1997, based on adverse event reports linked to dietary supplements containing ephedrine, the FDA proposed a rule limiting its use. *See* Proposed Rule for Dietary Supplements Containing Ephedrine Alkaloids, 62 Fed. Reg. 30678 (June 4, 1997). The proposal faced substantial opposition from, among others, the General Accounting Office, which expressed concerns about the use of the adverse event reports in supporting the proposal. It concluded that the FDA needed to "provide stronger evidence on the relationship between the intake of dietary supplements containing ephedrine alkaloids and the occurrence of adverse reactions that support the proposed" rule. Withdrawal in Part of Proposed Rule on Dietary Supplements Containing Ephedrine Alkaloids, 65 Fed. Reg. 17474, at 17475 (Apr. 3, 2000). The FDA responded by withdrawing the proposal because of the insufficiency of the science behind the reports. *See id.* The agency banned ephedrine years later, after an extensive notice-and-comment period, but that experience illustrates the minimal value of case reports generally.

The case reports the Government is relying upon here are not meaningfully different. The people discussed in the reports ingested

other substances, had pre-existing health conditions, or consumed DMAA at far greater amounts than recommended. *See, e.g.*, Doc. 108-4 at pp. 67-74, ¶¶84-93; Doc. 108-6 at pp. 230-245, ¶¶85-112. In one report, the author "reported four cases of cerebral stroke that occurred temporally with recreational use of DMAA as a party drug at doses up to ten times higher than would be recommended in dietary supplements." Doc. 108-4 at pp. 70-71, ¶89 & Doc. 108-6 at pp. 230-233, ¶86 (citing Gee et al., 2010, 2012). Three of the four individuals also had consumed alcohol. *See id.*

Another case report cited by the Government involved a 26-year-old soldier who experienced a stroke. The Government refers to this report as a "scientific stud[y]" in support of its argument that "DMAA may cause, or at least is correlated with, significant deleterious effects on people's health." U.S. Br. 35. But that report established no such causation or correlation. The soldier's stroke happened after consuming three times the recommended dose of DMAA-containing supplement. *See* Doc. 108-4 at pp. 71-72, ¶90 (summarizing Young 2012 study). His medical history revealed that he smoked heavily and took an unidentified hormone supplement. *See id.* Because of these factors and others,

the report concluded that it was "unclear whether the hemorrhagic stroke was a result of dietary supplement use or other predisposing factors, and suggested that consumption of the DMAA-containing supplement could have been merely coincidental and not causal." *Id.*

These and other case reports amount to, as Hi-Tech and Wheat's expert testified, "anecdotal observations that generally lack dose measurements or estimates, evaluation of pre-existing conditions, or confounding co-exposures to other compounds that are known to result in the reported health effect." *Id.* at p. 76, ¶94.3. Accordingly, that expert found "no evidence to indicate that consumption of DMAA at doses recommended in Hi-Tech's products would be sufficient to elicit adverse health effects described in the published case reports or implied by FDA." *Id.* at pp. 75-76, ¶94.2. That conclusion is bolstered by evidence suggesting that the total number of adverse events associated with people who have consumed DMAA is much smaller than the total number of adverse events associated with people who have taken supplements,

such as Vitamin C or multivitamins, that everyone knows to be safe. *See* Doc. 108-4 at pp. 78-81, ¶¶97-99; Doc. 108-6 at pp. 366-69, ¶¶75-81.[5]

For the Government's witness to so heavily rely upon these case reports was improper, and at the very least they could not create so conclusive an inference as to render summary judgment appropriate. Case reports can in certain circumstances be relevant to a GRAS determination. But even the Government's expert conceded that a substance could "potentially cause harm to somebody" yet "still be generally recognized as safe." Doc. 108-6 at p. 22, tr. 54:20-25. He also acknowledged that "something that's GRAS can have a toxic effect at a

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[5] Particularly in light of the other evidence in the record, the Department of Defense's decision to bar DMAA sales on military bases would not have precluded a fact-finder from determining that the scientific community generally recognizes DMAA to be safe when used at its intended doses. *See* U.S. Br. 35-36. The Department's examiners found that two of the service members who had died had sickle-cell trait, two were obese, and one had extensive coronary artery disease. *See* Doc. 107-5 at pp. 187-89. None had high levels of DMAA in their blood, which led the Department to find that "it is unlikely that DMAA played a significant role in these four deaths." *Id.* Because "[t]he existing evidence does not conclusively establish that DMAA-containing substances are causally-associated with adverse medical events," the Department recommended further study. *Id.* at p. 172. It recommended barring sales for a host of reasons that included not only the service members' deaths but also concerns that allowing sales would suggest that command was encouraging soldiers to use dietary supplements. *See id.*

sufficient dose." *Id.* at p. 30, tr. 86:6-13. His testimony was insufficient to rebut the evidence Hi-Tech and Wheat offered that DMAA is generally recognized as safe.

* * *

The weakness of the Government's evidence on the second question presented underscores the fundamental concerns of agency overreach that permeate both aspects of this appeal. As the evidence discussed above suggests, the FDA could not have made the showing necessary to ban DMAA on the premise that it presents "significant risk of illness or injury." 21 U.S.C. § 342(f)(1)(A). So the agency, in reliance on the Mississippi and Texas studies, claimed that DMAA was not a "dietary ingredient" and tried to shift the burden to Hi-Tech and Wheat to establish that DMAA is generally recognized as safe. Hi-Tech and Wheat established that the Mississippi and Texas studies were flawed and that DMAA is a dietary ingredient. But Hi-Tech and Wheat also satisfied the additional burden the agency foisted upon it, offering four experts who focused on reliable studies and testified to DMAA's safety. Yet after benefiting from the District Court's *sua sponte* and erroneous interpretation of "dietary ingredient," the Government obtained sum-

mary judgment on GRAS based on a single witness's testimony focusing on case reports. DSHEA did not allow the Government to shift the burden of proving DMAA's safety in that way. But if the Government were allowed to do so, a safety showing like the one Hi-Tech and Wheat made should have at least required a trial.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This brief complies with the applicable type-volume limitation under Rule 32(a)(7) of the Federal Rules of Appellate Procedure and 11th Circuit Rule 32-4. According to the word count in Microsoft Word 2010, the relevant parts of this brief contain 6,249 words. This brief complies with the applicable type-style requirements limitation under Rule 32 of the Federal Rules of Appellate Procedure. I prepared this brief in a proportionally spaced Century Schoolbook font sized 14 point or, for headings, with a larger point size.

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CERTIFICATE OF SERVICE

On January 25, 2018, I efiled this brief with the Court via CM-ECF, which will serve the following attorneys for the United States:

Daniel Aguilar
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On the same day, I mailed seven copies to the Court via First Class United States Mail, postage prepaid.

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