No. 05-4151

IN THE UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

NUTRACEUTICAL CORPORATION, et al.,
Plaintiffs-Appellees,

v.

ANDREW VON ESCHENBACH, Acting Commissioner,
U.S. Food and Drug Administration, et al.,
Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF UTAH
The Honorable Tena Campbell

APPELLEES' PETITION FOR REHEARING OR REHEARING EN BANC

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Nutraceutical Corporation and Solaray, Inc. (Nutraceutical) hereby petition for rehearing or rehearing *en banc* of the panel decision filed Aug. 17, 2006. See Exhibit A.

STATEMENT OF COUNSEL UNDER F.R.A.P. 35(b)

The Decision raises the following questions of exceptional importance:

(1) Whether the panel's decision upholding the Food and Drug Administration's (FDA's) ban on ephedrine alkaloids at all dose levels in dietary supplements but permitting their sale at all dose levels in foods renders the Food Adulteration provision of the Dietary Supplement Health and Education Act of 1994 (DSHEA) internally inconsistent and irrational contrary to the intent of Congress and the canons of statutory construction;

(2) Whether the panel's reliance on argument not in the FDA Rule and first raised by FDA before the panel (that the definition of "unreasonable risk" in the Food Drug and Cosmetic Act's (FDCA's) Food Adulteration section should be the same as that for the term in the FDCA's New Drugs section) is an impermissible *post hoc* rationalization;

(3) Whether the risk-benefit analysis in the panel's definition of "unreasonable risk" improperly allows the FDA in its post-market review to subject dietary supplements, a form of food under the Act, to safety and effectiveness standards that are reserved to the pre-market review of drugs, all in manifest conflict with the DSHEA;

(4) Whether the panel's definition of "unreasonable risk" grants the FDA virtually unbridled discretion to remove any dietary ingredient from the market in manifest conflict with the DSHEA.

The Decision conflicts with the Supreme Court's precedent governing statutory construction.[1]

[1] Those cases are Gonzales v. Oregon, 126 S.Ct. 904, 925 (2006); Whitaker v. American Trucking Ass'n, 531 U.S. 457, 468 (2001); FDA v. Brown & Williamson Tobacco, 529 U.S. 120, 133 (2000); Estate of Cowart v. Nicklos Drilling Co., 505 U.S. 469, 475 (1992); Demarest v. Manspeaker, 498 U.S. 184, 190 (1991); Chevron USA Inc. v. Natural Resources Defense Council Inc., 467 U.S. 837, 842 (1984); and Russello v. United States, 464 U.S. 16, 23 (1983).

BACKGROUND AND INTRODUCTION

In 1994, Congress amended the FDCA, 21 USC 321 *et seq.*, with the DSHEA, Pub.L.No. 103-417, 108 Stat. 4325 (1994). The DSHEA declares dietary supplements (with one inapplicable exception) "foods" within the meaning of the FDCA. 21 USC 321(ff). In the Food Adulteration section, 21 USC 342, a dietary ingredient is adulterated (and unmarketable) if it "presents a significant or unreasonable risk of illness or injury under (i) conditions of use recommended or suggested in labeling . . ." 21 USC 342(f)(1)(A)(i). In a 2004 Rule FDA banned EDS at every dose level when present in dietary supplements (but excepted ephedrine alkaloids regardless of dose when present in foods) based on its reading of "unreasonable risk" in section 342(f)(1)(A)(i) of the Food Adulteration section of the Act. 69 Fed.Reg. 6788, 6793 (Feb. 11, 2004). At trial and on appeal, this case turned on construction of "unreasonable risk." Nutraceutical v. Crawford, 364 F.Supp.2d 1310, 1318 (D.Ut. 2005) and Op. at 10. The District Court and the panel each held "unreasonable risk" unambiguous, yet reached opposite conclusions as to its "clear" meaning. Op. at 10-11; 364 F.Supp.2d at 1318. Nutraceutical is unaware of any prior case in which two courts have applied Chevron Step 1 to the same statutory language but have reached precisely opposite determinations of meaning.

The District Court held FDA's Rule a violation of section 342(f)(1)(A)(i), explaining that the Rule depended on a risk-benefit comparison when nowhere in the Food Title does Congress grant FDA authority to counterbalance risks with benefits; rather, by its terms section 342(f)(1)(A)(i) only mentions risk. The District Court also held, consistent with the statutory language ("conditions of use recommended or

suggested in labeling") that FDA had to evaluate the actual dietary ingredient, not a hypothetical drug substitute, under actual conditions of use and determine the dose level at which injury occurred (banning ephedrine alkaloids at that dose and above). The panel reversed, upholding FDA's interpretation of "unreasonable risk," relying on Merck KGaA v. Integra-Life Sciences I, Ltd., 125 S.Ct. 2372 (2005) (citing 21 USC 355(i)(3)(B)(i), the New Drugs' section of the Act), Op. at 11, and accepting as valid FDA's reliance on a hypothetical drug model, not on the actual dietary ingredient at actual dose levels. Op. at 17-19.

The panel decision effectively imposes the same risk-benefit comparison standard in post-market review of dietary supplements that is reserved by statute for pre-market review of drugs. The decision's impact extends far beyond a ban on EDS. It grants FDA authority to declare any dietary ingredient adulterated on FDA's subjective assessment of the adequacy of the ingredient's health benefits if FDA finds even so much as an infinitesimal risk of illness or injury from ingestion of the ingredient (a ubiquitous condition because all ingredients pose some risk at some dose).

The 1962 Kefauver-Harris Amendments to the FDCA decree that no drug may lawfully enter the market unless FDA finds it safe and effective. Without any support from text or legislative history, the panel invoked the surplusage canon (no term should be treated as surplusage) to read the drug effectiveness requirement into the food provisions of the Act governing dietary ingredients. Moreover, the panel condoned FDA's application of that standard. At no point did FDA determine whether the recommended concentrations at which EDS was sold (10 mg or less/day) posed the

unreasonable risk it purported to measure. Instead it evaded its burden of proof by allowing extrapolations of risk to be made from the study of different substances (the drugs epinephrine and ephedrine) in different concentrations and through different methods of administration (continuous IV drip rather than oral ingestion). The Rule forbids Nutraceutical from selling its low-dose EDS in a dietary supplement but allows it to sell the very same substance (indeed, any amount of ephedrine alkaloids) in a tea bag. The Rule thus renders the Food Adulteration section irrational and internally inconsistent: what may not be sold as a dietary ingredient may be sold as a food.

In its Rule, FDA concluded that "unreasonable risk" meant "comparison of the risks and benefits . . . ," 69 Fed.Reg. at 6823, "a relative weighing of the product's known and reasonably likely risks against its known and reasonably likely benefits." Id. FDA stated that "significant" and "unreasonable" had distinct meanings. "Significant" involved risk alone, while "unreasonable" required a risk-benefit comparison, reasoning that "[a] risk could be significant, but reasonable, if the benefits were great enough to outweigh the risks." Id. The FDA deemed it unnecessary to determine if EDS presented a "significant" risk, basing its decision exclusively on "unreasonable" risk. Id. at 6788; 6822-23. FDA declared "[i]n the absence of a sufficient benefit, the presence of even a relatively small risk . . . may be unreasonable." Id. at 6788. FDA concluded that EDS pose short and long-term risks and "[t]he data do not indicate that these products provide

a health benefit sufficient to outweigh these risks." Id. at 6789. There was no mention of any other consumer benefits.[2] Therefore, FDA banned all EDS as "adulterated."

In its Rule and before the District Court, FDA relied on the FDCA's medical device classification section, 21 USC 360c(a)(2)(C) (not the medical device banning section, 21 USC 360(f), and not the New Drugs section, 21 USC 355(i)(3)(B)(i)), as support for its argument that "unreasonable risk" meant a risk-benefit comparison. See 69 Fed.Reg. at 6823; 364 F.Supp.2d at 1318. That section, however, does not use the term "unreasonable risk" and pertains to pre-market classification of medical devices. 21 USC 360c(a)(2)(C).

Before the panel, FDA shifted its reliance to the New Drugs section in 21 USC 355(i)(3)(B)(i), citing to Merck, 125 S.Ct. at 238. The panel agreed with FDA, also citing Merck, Op. at 11, holding under Chevron Step 1 that "unreasonable risk" meant the same as in the New Drugs section. The New Drugs section in Merck[3] deals with patent issues far removed from this dispute. Given these manifest differences, it is unsurprising that neither the FDA Rule nor FDA in District Court relied on that New Drugs section to

[2] Assuming *arguendo* "unreasonable" means a risk-benefit comparison, FDA's approach is still illogical. There is nothing in the term that requires FDA to ignore all other benefits consumers attach to the consumption of a dietary supplement. The technical measure of consumer welfare is equal to the price that consumers collectively would pay over its cost in order to consume the product in question. Those subjective and psychic components belong on the benefit side of any risk-benefit equation. But once those are included, there is no basis for holding that a dietary supplement with an infinitesimal risk does not produce a net benefit. That conclusion would not be proper for other foods, like the potato chip example cited by the District Court, 364 F.Supp.2d at 1319 n.6, governed under the identical statute.

[3] In Merck, the Court examined 21 USC 355(i)(3)(B)(i), along with others, to determine the scope of a safe harbor from patent infringement for preclinical testing necessary to supply FDA information on a new drug. 125 S.Ct. at 2380-2381.

define "unreasonable risk." Rather, FDA first raised the argument before the panel. The panel's reliance on that *post hoc* rationalization is forbidden. See, e.g., Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 419 (1971).

THE PANEL DECISION

The panel observed that "Congress enacted DSHEA to clarify that dietary supplements . . . would be regulated . . . similar to food[s]," Op. at 11, and "to improve public access to . . . supplements . . ." Id. (citation omitted). However, when the panel addressed the meaning of "unreasonable risk," it disregarded those principles and misinterpreted the statute. The panel engaged in a statutory tour-de-force, holding that Chevron Step 1 required approval of the same statutory scheme that the District Court struck down on summary judgment. In making this 180° switch, the panel held FDA had manifest authority to evaluate the health benefits of dietary ingredients even for dietary ingredients with an infinitesimal risk. The sole peg for the panel's rendition was its aggressive reading of the words "unreasonable risk" within the following phrase in 21 USC 342(f)(1)(A)(i): "presents a significant or unreasonable risk of illness or injury under – (i) conditions of use recommended or suggested in labeling." At trial and on appeal, the case turned on the words "unreasonable risk." Nutraceutical, 364 F.Supp.2d at 1318 and Op. at 10.

In the panel's view the single canon governing construction is that of "surplusage." That formalist canon insists that each word within a provision carry a meaning distinct from all others. The term "significant risk" clearly refers to risk magnitude and ensures that miniscule risks associated with tiny levels of ingestion do not

constitute adulteration. The panel held the term "unreasonable risk" meant exclusively a risk-benefit comparison as prescribed in the New Drugs section of the Act, Op. at 11; however, by plain meaning in context the term does not beget that definition. In context, a risk is unreasonable when a dietary ingredient reaches a dose level that causes illness or injury.[4] The surplusage canon may not be used to effect a meaning contrary to the one plainly intended and here, without question, importation of the drug risk-benefit standard into the food context violates Congress's plain intent.[5] The panel reads "unreasonable risk" out of context to require thorough investigation of dietary ingredient health benefits. In so doing, it morphed the Food Adulteration section into the effectiveness review that the FDCA requires only of drugs. That statutory tour-de-force reads out of section 342(f)(1)(A)(i) the requirement that adulteration be based on recommended or suggested dosage (allowing adulteration to exist without a showing of harm at a particular dose and recommended use).

Neither section 342(f)(1)(A) nor any DSHEA part mentions "potential benefits" in determining whether a risk is unreasonable. The panel's only authority for its conclusion

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[4] By contrast, a "significant" risk is one that describes the degree of illness or injury incurred (e.g., a tumor as opposed to a headache).

[5] The surplusage canon cannot be used to interpret the law contrary to congressional intent. Scheidler v. National Organization for Women, Inc., 126 S.Ct. 1264, 1273-1274 (2006); see also Lamie v. United States Trustee, 540 U.S. 526, (2004)(citing Chickasaw Nation v. United States, 534 U.S. 84, 94 (2001)). Congress has made it crystal clear that dietary supplements are to be regulated as foods, not drugs. 21 U.S.C. 321(ff); see discussion 10-11 infra. Foods are not required to prove a benefit when faced with a claim of adulteration. 21 U.S.C. 342. In FDA's pre-market evaluation, drugs are required to prove a benefit to weigh against risk of harm. 21 U.S.C. 355(a).

is the drug case Merck. Op. at 11. Merck involved the meaning of "unreasonable risk" in the "clinical hold" exception to the FDCA's New Drugs section. See 21 USC 355(i)(3)(B)(i). To be sure, the FDCA expressly requires FDA to undertake a risk-benefit evaluation of new drugs, see 21 USC 355(b)(1)(A), so it is hardly surprising that the FDA regulation on point, 21 CFR 56.111(a)(2)(2006), would incorporate a risk-benefit test. By contrast, DSHEA includes no comparable express statutory provision for a risk-benefit analysis of supplements. Merck is therefore inapposite.

The panel's interpretation of "unreasonable risk" utterly undermines the section's systematic purpose by wrenching those two words out of context in ways that vastly expand the FDA's power over dietary supplements. Food adulteration law is grounded in the Paracelsian axiom that dose determines toxicity. All dietary ingredients pose a risk, depending on dose. Thus, with that essential distinguishing principle and the plain contextual meaning in mind, an "unreasonable risk" is defined as that dose level that causes illness or injury and above. A "significant" risk is one that describes the degree of illness or injury incurred (e.g., a tumor as opposed to a headache).

The panel accepted FDA's logic that even a slight risk justifies a finding of adulteration if no substantial countervailing benefit exists. 69 Fed. Reg. at 6788. Thus by giving "significant" no meaning, FDA may ban a dietary ingredient upon proof of even the slightest risk at some dose level. It is axiomatic, however, that all substances (even water) pose a risk at some dose level. See Fleming v. Florida Citrus Exchange, 358 U.S. 153, 163 (1958); see also United States v. Lexington Mill & Elevator Co., 232 U.S. 399, 411-412 (1914). Thus, the interpretation given removes from the law its dose

determines toxicity distinguishing principle, the principle that gives meaning to the "conditions of use" requirement in 21 USC 342(f)(1)(A)(i) (that risk be assessed based on the actual ingredient at doses recommended). On the panel's logic, there could be at most an infinitesimal risk of some injury and still the dietary ingredient would be unlawful if FDA opines that the health benefits of the ingredient are insubstantial. That rationale affords no real protection to supplements. It flouts DSHEA statutory findings that "dietary supplements are safe within a broad range of intake . . ." and that legislative action is needed to protect "the right of . . .consumers to safe dietary supplements . . ." Pub. L. 103-417, Sec. 2, Findings at paras. 14, 15(A). On the panel's logic, there is never a reason for FDA to deal with "significance" of risk. Op. at 14. Risk significance is immaterial (any risk will do). The dose determines toxicity concept has been written out of the law; regardless of dose, a slight risk at some dose in the absence of a substantial benefit is now grounds for finding adulteration.[6]

In addition, the aggressive reading of this provision undermines the requirement that FDA bear the burden of proof to demonstrate that the dietary ingredient is adulterated under the statute for its use at a specific concentration. 21 USC 342. That individuated determination cannot be supported by extrapolating from studies not

[6] Because the statute places the burden of proof on FDA, 21 USC 342(f)(1), the shift from proof of risk significance to benefit significance causes the overall adulteration determination to turn on the extent of benefit, not of risk. The risk side of the equation is a given; the ultimate outcome is now to be decided based on FDA's subjective perception of benefit.

involving any field or clinical findings concerning the specific dietary ingredient at the dosages recommended.[7]

ARGUMENT

C. The Panel's "Unreasonable Risk" Definition Violates the Supreme Court's Statutory Construction Precedent

FDCA's Food Adulteration section nowhere mentions a comparison of risks and benefits. The panel nevertheless holds "unreasonable risk" "to connote" that comparison not based on precedent governing dietary ingredients but based on precedent governing new drugs. The panel thus reaches beyond anything in the Act that governs foods to the New Drugs section for a definition that will govern when a dietary ingredient may be removed from the market. That reach goes too far. It upsets the statutory distinction between foods, including dietary ingredients (which are presumed safe and marketable based on historic use in the food supply), and drugs (which are presumed unsafe and unmarketable until proof of efficacy is shown to exceed proof of risk). See 21 USC 342, 350b, 321(p), 355.

The FDCA creates distinct food and drug regulatory regimes. Foods need only be safe to be marketed (proof of benefit is not required). See 21 USC 342. Drugs must be both safe and efficacious (proof of efficacy is required). 21 USC 321(p), 355. Dietary ingredient adulteration arises in the Food Adulteration section (21 USC 342; 342(f)). The

[7] Nutraceutical's argument is bolstered by the detailed committee report for this statute which at every point reveals Congress's antipathy toward FDA's efforts to restrict the availability of dietary supplements. At several points the report affirms the soundness of decisions rebuking FDA for its aggressive positions, S.Rep. 103-410, at 21, 22 (1994), agreeing with the description of the Circuit Courts deeming FDA's actions "nonsense" and an "Alice-in-Wonderland" approach.

FDCA deems supplements "food[s] within the meaning of this Act." 21 USC 321(ff). There is no FDCA language (and none in the legislative history, S. Rep. 103-410 (1994)) directing FDA to treat dietary ingredients like drugs for adulteration purposes. To the contrary, Congress insists that dietary supplements be regulated as "foods:" "[Section 321(ff)] is intended to be explicit about a point that ought to be clear . . . : a product intended . . . to supplement the diet with any . . . herb . . . is subject to regulation as a food and not as a drug," S. Rep. 103-410 at 19; ". . . FDA has attempted . . . to assert that . . . dietary ingredients are drugs based solely on their composition . . . [;] [t]his has led to inconsistent . . . treatment of . . . supplements as drugs . . . ," Id. at 19; and "[t]he committee intends that . . . FDA . . . regulate dietary supplements as food . . . not as drugs . . ." Id. at 20.[8] There is no FDCA language directing FDA to abandon its focus in food adulteration on risk of the dietary ingredient under actual conditions of use.[9]

[8] In a "Statement of Agreement" in the congressional record after the Senate Report but before the vote on DSHEA, nine bill sponsors stated their "intent" that "no other reports or statements be considered as legislative history for the bill." 140 Cong. Rec. S14801 (Oct. 7, 1994), reprinted in 1994 U.S.C.C.A.N. 352. The Statement is invalid as an attempt to replace the Senate Report; the opinion of nine bill sponsors, *after* the Senate Report in support of the bill was voted out of committee, cannot undo the legislative significance of that majority committee report. See Garcia v. United States, 469 U.S. 70, 76, 76n.3 (1984) (authoritative source for legislative history is the committee reports, not floor statements). In Pharmanex v. Shalala, 221 F.3d 1151, 1158 (10th Cir. 2000), this court recognized the Statement of Agreement, expressly did not "pass[] on the legitimacy or effectiveness of" it, 221 F.3d at 1158, and considered the Senate Report despite it. Id.

[9] See, e.g., United States v. Anderson Seafoods, 622 F.2d 157, 162 (5th Cir. 1980) (FDA failed to prove mercury adulteration in fish because agency relied not on actual conditions but on general mercury science); United States v. Boston Farm Center, 590 F.2d 149 (5th Cir. 1974) (FDA failed to prove aflatoxin adulteration in corn because agency relied not on actual conditions but on general aflatoxins science).

In construing statutory language, the Supreme Court expects agencies to give effect to every word, not render words such as "significant" and "conditions of use recommended or suggested in labeling" meaningless. See Estate of Cowart, 505 U.S. at 475 (citing Demarest, 498 U.S. at 190). The Court presumes Congress intends no fundamental change in existing law unless Congress makes that intention clear in the language of the Act itself. See Gonzales, 126 S.Ct. at 925; see also American Trucking Ass'n, 531 U.S. at 468 ("Congress . . . does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not, one might say, hide elephants in mouseholes"). Here the shift from risk (the historic food model) to a comparison of risk and benefit (the historic drug mode of analysis) is, pure and simple, an extra-statutory reach by FDA, a raw usurpation that treats the term "unreasonable" as the proverbial elephant in the mousehole. The Supreme Court instructs that "where Congress includes particular language in one section of a statute but omits it in another . . ., it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." Russello, 464 U.S. at 23. Surely had Congress intended so radical a move as the adoption of the New Drugs risk-benefit analysis for dietary ingredient adulteration, it would have said so plainly in the Act,[10] by using parallel provisions to the effectiveness language that Kefauver-Harris introduced for drugs. The Supreme Court expects statutes to be interpreted to be rational; the law abhors internal

[10] The absence of language directing FDA to adopt risk-benefit is telling because elsewhere when Congress intended that interpretation it supplied it expressly. Cf. 21 USC 342(f)(1)(A)(i) and 21 USC 360c. See also American Textile Mfr. Inst. v. Donovan, 452 U.S. 490, 510 (1981)(When Congress intends a cost-benefit analysis, it indicates that intent "on the face of the statute").

inconsistency. See Brown & Williamson Tobacco Corp, 529 U.S. at 133 (courts must interpret the statute "'as a symmetrical and coherent regulatory scheme' and 'fit, if possible, all parts into a harmonious whole'") (citations omitted). FDA's Rule produces the absurd result of causing raw crushed ephedra sinica herb to be unlawful when placed in a gelatin capsule but legal when placed in a tea bag. The Rule thus renders the Food Adulteration provision internally inconsistent. Dietary ingredients in supplements are held to a drug risk-benefit standard but the very same ingredients in foods are held exclusively to a risk standard.

D. The Panel's Decision Involves Questions of Exceptional Importance

In DSHEA Section 2 (Findings), Congress explained that nearly "50 percent of . . . Americans regularly consume dietary supplements" and that the supplement industry is "an integral part of the [U.S.] economy . . ." Pub. L. 103-417, 108 Stat. 4325, 4326 ((9) and (12)(A)). Congress meant to protect public access to dietary ingredients at safe dose levels. 108 Stat. at 4326 (15)(A); S.Rep. 103-410 at 36 ("a safety finding cannot be entered against a supplement based upon a dosage not recommended in the labeling"). The Rule upheld by the panel is the first to ban a dietary ingredient at every dose level based on an assessment in which even a slight risk is sufficient to justify that draconian action unless FDA finds a substantial countervailing benefit. With that low risk threshold and subjective benefit balancing—a test liberated from the need to prove the dose at which toxicity occurs—FDA may in its discretion remove virtually any

dietary ingredient from the market.[11] To quote FDA, "[i]n the absence of a sufficient benefit, the presence of even a relatively small risk . . . may be unreasonable." 69 Fed.Reg. at 6788.[12] Small, for these purposes, means any risk greater than zero, which is any risk at all.

The panel has given FDA unprecedented power to declare a dietary ingredient adulterated even down to a molecule (i.e., even at unquestionably safe doses) when proof of illness or injury only exists at many times that dose. The result is an extraordinary power to constrict the availability of dietary ingredients even at safe doses, an end opposite the DSHEA aim of protecting consumer access to supplements at those doses.

Moreover, the argument that "unreasonable risk" "obviously" connotes exclusively a risk-benefit comparison is belied by FDA's shifting reliance. In the Rule

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[11] The Rule banned all EDS, even down to a molecule. The ban is not based on testing of the actual dietary ingredient at Nutraceutical's dose (10mg or less/day) as required by the statute ("under conditions of use recommended . . . in labeling," 21 USC 342(f)(1)(A)(i)) but on a hypothetical drug comparison model, an untested, unpeer-reviewed extrapolation from unrelated tests of the drugs epinephrine and ephedrine to the dietary ingredient ephedrine alkaloids. In unpeer-reviewed letters, one Dr. Mario Inchiosa speculated from intravenous drug studies that the pharmacologically different non-drug substance, ephedrine alkaloids, when orally ingested at 1.5 mg every four hours continuously would raise heart rate and blood pressure akin to the drugs. Appellants' App. at 218. The proof did not test the dietary ingredient at all, let alone at specific doses recommended in labeling. Reliance on hypothetical drug comparison models does not satisfy FDA's "burden of proof on each element" including "conditions of use recommended . . . in labeling" required by the statute.

[12] The Paracelsian dose determines toxicity axiom, articulated in the Supreme Court's earliest food adulteration decision, Lexington Mill & Elevator Co., 232 U.S. at 411-412, and reiterated in food decisions ever since (see, e.g., Anderson Seafoods, 622 F.2d 159) is the irreducible distinguishing principle in determining whether a food or dietary ingredient based on conditions of use is adulterated. Risk is immaterial until we reach that dose at which illness or injury occurs. The division between a lawful and an adulterated dietary ingredient is that very dose level and above.

and before the District Court, FDA argued "unreasonable risk" meant the same as Congress provided in the medical device classification section, 21 USC 360c (where, in fact, the term "unreasonable risk" does not appear), and meant the same as Congress specified in the Toxic Substances Control Act despite the obvious inapplicability of that law to the FDCA. On appeal, however, FDA shifted its reliance with a *post hoc* rationalization: identifying the New Drugs section's clinical hold exception (cited in Merck, 125 S.Ct. 2372) as defining "unreasonable risk." The panel agreed with FDA and relied on that same drug section, thus causing arguments first raised on appeal to be accepted as the decisional rationale, *post hoc*, when the Rule contains no such basis. The courts of appeal, including this court, prohibit *post hoc* rationalizations of this kind;[13] the panel decision is predicated centrally on this forbidden rationale.

CONCLUSION

For the foregoing reasons, Nutraceutical Corporation respectfully requests that this Honorable Court grant rehearing or rehearing en banc of the panel decision.

Respectfully submitted,
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SOLARAY, INC.

By:_____/s/_____

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[13] The record on appeal of an administrative agency rulemaking is "frozen." Neither the FDA nor parties appealing the rule may introduce for the first time *post hoc* rationalizations for the rule. See Citizens to Preserve Overton Park, 401 U.S. at 419 (citations omitted).

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Dated: September 28, 2006

CERTIFICATION OF DIGITAL SUBMISSIONS

In accordance with the Court's Emergency General Order, as amended January 1, 2006, I certify the following:

1. No privacy redactions are required for or have been made in this document.
2. This document as submitted in digital form is an exact copy of the written document filed with the clerk of the court.
3. The digital submission of this document has been scanned for viruses with Symantec AV Enterprise 8.1, with the latest virus definitions, last updated September 27, 2006 and, according to that program, this document is free of viruses.

_____/s/_____
Jonathan W. Emord
Counsel for Appellees

CERTIFICATE OF SERVICE

I certify that on September 28th, 2006 I served the electronic copy of the foregoing Appellees' Petition for Rehearing or Rehearing En Banc and its attached Opinion of the Panel in Digital Form upon the Clerk of the U.S. Court of Appeals for the Tenth Circuit. I caused the original and eighteen copies to be filed with the Clerk by overnight mail on September 28th, 2006 for receipt on September 29th, 2006. I also served one copy upon the counsel listed below by UPS overnight mail and electronic mail.

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IN THE UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

NUTRACEUTICAL CORPORATION, et al., **Plaintiffs-Appellees,** **v.** **ANDREW VON ESCHENBACH, M.D., Acting Commissioner, U.S. Food and Drug Administration, et al.,** **Defendants-Appellants.**	**Docket No. 05-4151**

EXHIBIT A TO APPELLEES' PETITION FOR REHEARING
OR REHEARING EN BANC

THE PANEL OPINION ATTACHED IN ACCORDANCE WITH
10TH Cir.R. 40.2

F I L E D
United States Court of Appeals
Tenth Circuit

August 17, 2006

Elisabeth A. Shumaker
Clerk of Court

PUBLISH

UNITED STATES COURT OF APPEALS

TENTH CIRCUIT

NUTRACEUTICAL CORPORATION; SOLARAY, INC.,

Plaintiffs-Appellees,

v.

ANDREW VON ESCHENBACH, Acting Commissioner, U.S. Food and Drug Administration; UNITED STATES FOOD AND DRUG ADMINISTRATION; MICHAEL O. LEAVITT, Secretary of the Department of Health and Human Services; DEPARTMENT OF HEALTH AND HUMAN SERVICES; UNITED STATES OF AMERICA,

Defendants-Appellants.

No. 05-4151

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF UTAH
(D.C. No. 2:04-CV-00409-TC)

Christine N. Kohl, Attorney (Peter D. Keisler, Assistant Attorney General, Paul M. Warner, United States Attorney, Jeffrey Bucholtz, Deputy Assistant Attorney General, and Douglas N. Letter, Attorney, Department of Justice, Washington, D.C., and Paula M. Stannard, Acting General Counsel, Sheldon T. Bradshaw, Associate General Counsel, Eric M. Blumberg, Deputy Chief Counsel, and Claudia J. Zuckerman, Associate Chief Counsel, Office of General Counsel, U.S. Department of Health & Human Services, Food and Drug Division, Rockville, Maryland, with her on the briefs), for Defendants-Appellants.

Jonathan W. Emord (Andrea G. Ferrenz with him on the brief), Emord & Associates, P.C., Reston, Virginia for Plaintiffs-Appellees.

Before **KELLY, TYMKOVICH**, Circuit Judges and **EAGAN**,[*] District Judge.

EAGAN, District Judge.

Defendants-appellants, Andrew von Eschenbach, M.D., Acting Commissioner of the U.S. Food and Drug Administration, the United States Food and Drug Administration ("FDA" or "the agency"), Michael O. Leavitt, Secretary of the Department of Health and Human Services, the Department of Health and Human Services, and the United States, appeal from a judgment of the district court denying their motion for summary judgment and granting the cross-motion of plaintiffs-appellees for summary judgment. Nutraceutical Corp. v. Crawford, 364 F. Supp. 2d 1310 (D. Utah 2005). Plaintiffs-appellees, Nutraceutical Corporation and its wholly-owned subsidiary, Solaray Corporation (collectively,

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[*] The Honorable Claire V. Eagan, District Judge, United States District Court for the Northern District of Oklahoma, sitting by designation.

"Nutraceutical"), manufacture and sell Ephedra, a product containing ephedrine-alkaloid dietary supplements ("EDS"). In 2004, the FDA issued a regulation which banned all EDS sales in the United States market. Nutraceutical brought this action challenging the regulation as unlawful. The district court agreed with Nutraceutical. Id. at 1321. Our jurisdiction arises under 28 U.S.C. § 1291, and we reverse.

Background

In its published decision, the district court determined that the risk-benefit analysis employed by the FDA to support an EDS ban was contrary to the intent of Congress and that the FDA had failed to prove by a preponderance of the evidence that EDS pose an unreasonable risk of illness or injury at 10 milligrams ("mg") or less a day. Nutraceutical, 364 F. Supp. 2d 1310. It accordingly entered summary judgment in favor of Nutraceutical, enjoined the FDA from enforcing its proscription against Nutraceutical for the sale of products with a recommended daily dosage of 10 mg or less of EDS,[1] and remanded to the FDA for new rule-making.

The issues raised by this appeal are: (1) whether the FDA correctly interpreted the relevant statute to require a risk-benefit analysis in determining if a dietary supplement presents an "unreasonable risk of illness or injury"; and (2)

[1] To the extent that we recognize Nutraceutical's product as recommending less than 10 mg of ephedrine alkaloids per day, Nutraceutical's Motion to Correct Oral Argument Record, filed on May 11, 2006, is granted.

whether the FDA satisfied its burden of proving that dietary supplements containing EDS present an unreasonable risk of illness or injury when doses of 10 mg or less per day are suggested or recommended in labeling.

Nutraceutical alleges that the FDA lacked statutory authority to promulgate and enforce a ban of all EDS. The FDA argues that it acted pursuant to the broad authority delegated to it by the Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301, et seq., to regulate dietary supplements for safety. The FDCA provides the FDA with broad authority to regulate food, drug, and dietary supplement products in order to ensure public health and safety. Id. In 1994, Congress amended the FDCA with the Dietary Supplement Heath and Education Act ("DSHEA"), Pub. L. No. 103-417, 108 Stat. 4325 (1994). Under DSHEA, the FDA regulates vitamins, minerals, herbs, amino acids, and other dietary substances. Dietary supplements are generally regulated in a manner similar to food and the FDA is authorized to prevent adulterated products from entering the market. See 21 U.S.C. § 331(a), (b), (c), (k) (adulteration and distribution of adulterated food are prohibited acts). Congress declared that a dietary supplement is "adulterated":

> If it is a dietary supplement or contains a dietary ingredient that--
> (A) presents a significant or unreasonable risk of illness or injury under--
> (i) conditions of use recommended or suggested in labeling, or
> (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use; . . .

21 U.S.C. § 342(f)(1). The FDA argues that EDS are adulterated and points to the "unreasonable risk of illness or injury" provision of DSHEA as the primary source of statutory authority for its EDS ban. 21 U.S.C. § 342(f)(1)(A).

Ephedrine alkaloids are a class of structurally-related chemical stimulants that occur naturally in some botanicals. In the 1980s and 1990s, manufacturers promoted the sale of EDS for weight loss and athletic performance enhancement. In the 1990s, the FDA received numerous Adverse Event Reports ("AERs") which documented harmful side effects, including heart attacks, strokes, seizures, and death, associated with EDS intake.[2] Based on the circumstantial evidence of the AERs, the FDA began to investigate the effects of EDS. The investigation included a literature review of scientific studies and a Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids Meeting held on August 26-27, 1996 ("1996 Food Advisory Committee"). In 1997, the agency proposed a regulation which would have required specific warnings and established a dosage regimen. 62 Fed. Reg. 30,678 (June 4, 1997).

The FDA's 1997 proposed regulation of EDS faced substantial opposition, including from the General Accounting Office ("GAO"). The GAO determined that the FDA had not been thorough in its investigation and requested further

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[2] The FDA established the MedWatch program to monitor AERs associated with nutritional products, including dietary supplements. This program relies on voluntary reporting from public health agencies, health professionals, and consumers. See FDA MedWatch Home Page, http://www.fda.gov/medwatch/.

research. See GAO, Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids 11 (1999). Responding to the GAO's concerns, the FDA withdrew the 1997 proposed regulation. 65 Fed. Reg. 17,474 (Apr. 3, 2000).

The FDA continued to receive AERs and compile scientific literature regarding EDS. Given the fact that dietary supplement manufacturers are not required to submit scientific data on their products, the body of scientific literature on EDS was limited. Among the studies on which the FDA relied was a report commissioned by the National Institutes of Health. To further supplement the record, the agency hired Mario A. Inchiosa, Jr., Ph.D.,[3] to conduct further research on the health effects of EDS in 1999. During the public notice and comment period, Nutraceutical submitted to the FDA several requests for an exemption of low-dosage EDS, to no avail. The administrative record grew to over 130,000 pages, approximately 19,000 AERs were collected,[4] and extensive public notice and comment resulted in over 48,000 comments.

After seven years of investigating EDS, the FDA adopted a regulation which banned EDS at all dosage levels from the national market. Final Rule

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[3] Professor of Pharmacology, New York Medical College.

[4] The AERs which were voluntarily submitted to the FDA were supplemented with 16,000 complaints received by Metabolife, one of the largest distributors of EDS. 364 F. Supp. 2d at 1315; see GAO, Dietary Supplements: Review of Health-Related Call Records for Users of Metabolife 356 (GAO-03-494) (2003).

Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (Feb. 11, 2004) ("Final Rule"). In the Final Rule, the FDA concluded that "[t]he best clinical evidence for a benefit . . . supports only a modest short-term weight loss, insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese." Id. at 6789. Based on this risk-benefit analysis, the FDA determined that all EDS present an "unreasonable risk of illness or injury" under all ordinary or recommended conditions of use. Id. at 6788. As such, the Final Rule classified EDS adulterated within the meaning of DSHEA.

The district court held that "the FDA's requirement that EDS demonstrate a benefit is contrary to the clear intent of Congress" and found the agency's definition of "unreasonable" as entailing a risk-benefit analysis to be improper. 364 F. Supp. 2d 1310, 1319. The district court also found that the FDA failed "to prove by a preponderance of the evidence that a dosage of 10 mg or less of ephedrine alkaloids presents a significant or unreasonable risk of illness or injury." Id. at 1321. Based on these findings, the district court granted summary judgment for plaintiffs and denied summary judgment for defendants.

Discussion

Standard of Review

The district court's conclusions as to whether the FDA had acted pursuant to congressionally delegated authority in promulgating a rule is reviewed de novo. However, the parties dispute the appropriate standard of review of the administrative decision. DSHEA provides that: "The court shall decide any issue under this paragraph on a de novo basis." 21 U.S.C. § 342(f). The district court did "not reach the question of whether the FDA's statutory construction should be reviewed de novo." 364 F. Supp. 2d at 1317. In the interest of clarity and consistency, we now reach this question.

Courts are to review agency actions under DSHEA using the "traditional tools of statutory construction." Pharmanex v. Shalala, 221 F.3d 1151, 1154 (10th Cir. 2000). The de novo standard, under section 342(f), applies to enforcement actions by the United States against manufacturers of dietary supplements. Such enforcement actions may result in imprisonment or monetary fines. 21 U.S.C. § 333; see United States v. Park, 421 U.S. 658 (1975). Reading the statute as a whole, it is clear that the de novo standard applies when courts "decide" matters rather than when they "review" administrative decisions. As such, it is appropriate to limit the de novo standard of review, which affords the FDA no deference, to enforcement proceedings. Challenges by private parties to FDA rules promulgated under DSHEA are reviewed pursuant to the

Administrative Procedure Act ("APA"), 5 U.S.C. § 706, and "the normal rules for judicial deference regarding agency action apply." NVE, Inc. v. HHS, 436 F.3d 182, 196 (3rd Cir. 2006). "Had Congress intended to supplant the well-established procedures for APA challenges, it would have been clearer about its objective." Id. at 194.

Chevron Analysis

A court reviewing the FDA's construction of the FDCA must determine: whether Congress has directly spoken to precise question at issue; and if not, then whether agency's construction of statute is permissible one. Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837, 842-43 (1984). In reviewing the FDA's interpretation of DSHEA under Chevron, we ask two questions:

> First, always, is the question whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress [Chevron step 1]. But if the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute. If Congress has explicitly or implicitly delegated authority to an agency, legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute [Chevron step 2].

Seneca-Cayuga Tribe of Oklahoma v. National Indian Gaming Com'n, 327 F.3d 1019, 1037 (10th Cir. 2003) (citations omitted).

The APA reflects the principles of Chevron and "provides that agency action must be set aside if the action was 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law' or if the action failed to meet statutory, procedural, or constitutional requirements." Valley Cmty. Pres. Comm'n v. Mineta, 373 F.3d 1078, 1084 (10th Cir. 2004) (internal quotation omitted) (citing 5 U.S.C. § 706). "When we review an agency's decision under the arbitrary, capricious or abuse of discretion standard [of the APA], our review is narrow and deferential; we must uphold the agency's action if it has articulated a rational basis for the decision and has considered relevant factors." Slingluff v. Occupational Safety & Health Review Comm'n, 425 F.3d 861, 866 (10th Cir. 2005) (citing Mountain Side Mobile Estates P'ship v. Sec'y of HUD, 56 F.3d 1243, 1250 (10th Cir. 1995)). Under the APA, regulations are presumed to be valid, and review is deferential to the government agency.

"Unreasonable Risk"

In this case, we must determine whether Congress unambiguously manifested its intent to restrict the FDA from weighing benefits when determining the risk posed by a dietary supplement. The district court was correct to proceed under Chevron step one in deciding the question of whether the FDA properly used a risk-benefit analysis in determining whether EDS pose an "unreasonable risk." Chevron, 467 U.S. at 843. We nevertheless reverse the district court after

finding that Congress unambiguously required the FDA to conduct a risk-benefit analysis under DSHEA.

In 1994, Congress enacted DSHEA to clarify that dietary supplements, absent declarations promoting the supplements as drugs, would be regulated in a manner similar to food products. Accordingly, in the interest of public health, Congress imposed a duty on the FDA to keep adulterated dietary supplements off the market. 108 Stat. at 4326 (instructing the FDA to "take swift action against [dietary supplements] that are unsafe or adulterated."). DSHEA classifies a dietary supplement as adulterated if it "presents a significant or unreasonable risk of illness or injury." 21 U.S.C. § 342(f)(1). The FDA understood "[t]he plain meaning of 'unreasonable' . . . [to] connote[] comparison of the risks and benefits of the product." 69 Fed. Reg. 6788, 6823 (2004). We agree. The plain language of the statute directs the FDA to restrict distribution of dietary supplements which pose any risk that is unreasonable in light of its potential benefits. See Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005) (unanimously finding that "unreasonable risk," as used in another FDCA provision, 21 U.S.C. § 355(i)(3)(B)(I), "involves a comparison of the risks and the benefits . . . .").

Congress enacted DSHEA in an effort to improve public access to dietary supplements based on the belief that there may be a positive relationship between dietary supplement use, reduced health-care expenses, and disease prevention. See Pharmanex, 221 F.3d at 1158-59 ("It is true that DSHEA was enacted to

alleviate the regulatory burdens on the dietary supplement industry, allowing consumers greater access to safe dietary supplements in order to promote greater wellness among the American population.") (citation omitted). The FDCA should not be read too restrictively but in manner consistent with the statute's overriding purpose to protect public health. See 21 U.S.C.A. § 301 et seq.; United States v. Rx Depot, Inc., 438 F.3d 1052, 1061 (10th Cir. 2006) ("The FDCA's primary purpose is to protect the public health.") (citing United States v. An Article of Drug . . . Bacto-Unidisk, 394 U.S. 784, 798 (1969)). Accordingly, DSHEA should receive a liberal construction where the FDA has taken remedial steps in response to a perceived public health problem.

According to the district court, by injecting a risk-benefit analysis, the FDA required Nutraceutical to make a showing of the benefits of its product. However, at no time has the FDA required manufacturers of EDS to provide data on the benefits of their products. Rather, the FDA has assumed its responsibility of gathering data, soliciting comments, and conducting the risk-benefit analysis.[5]

[5] The district court compared the language of DSHEA to the statutory language governing medical devices and drugs and concluded that, unlike manufacturers of medical devices and drugs, manufacturers of dietary supplements do not need to prove effectiveness prior to taking their product to market. 364 F. Supp. 2d at 1318 ("A brief look at the legislative history of the DSHEA indicates that Congress generally intended to harmonize the treatment of dietary supplements with that of foods when it added the dietary supplement subsection to the food adulteration provision."). The district court is correct. However, the district court confused effectiveness with safety. The FDA did not ban EDS for failing to deliver promised health gains or for ineffectiveness; the FDA banned EDS because they were determined to be unsafe.

Congress expressly placed the burden of proof on the government to determine whether a dietary supplement is adulterated. Accordingly, EDS were allowed to enter the market without findings of safety or effectiveness. The FDA did not impose a pre-market requirement for the sale of EDS. For example, Nutraceutical has been selling EDS since 1988. As dictated by the statutory scheme, the FDA assumed the duty of post-market surveillance and imposed the EDS ban following numerous AERs, public notice and comment, and significant scientific review. See 69 Fed. Reg. 6788. Based on the record, we disagree with the district court and find that the FDA did not shift the burden of proof to manufacturers. The risk-benefit analysis is conducted by, and at the expense of, the agency. Id. at 6798 ("the agency performs a risk/benefit analysis to ascertain whether the risks of the product outweigh its benefits."). Despite Nutraceutical's characterization of the process, the agency did not "require[] proof of a substantial benefit to counterbalance risk as a condition precedent to lawful sale of EDS." Appellee's Brief, at 5. The burden remains on the agency to show that risks associated with a dietary supplement outweigh benefits and are, therefore, unreasonable. Thus, a risk-benefit analysis does not undermine congressional intent by improperly shifting the burden of proof onto manufacturers of dietary supplements.

Under the rules of statutory construction, courts consider the whole act and evaluate terms in context. Pharmanex, 221 F.3d at 1154 ("we examine the statutory provision in context."). The rule against surplusage encourages courts

to give meaning to every word used in a statute to realize congressional intent. In effect, this rule embodies the belief that Congress would not have included superfluous language. Thus, in DSHEA, an "unreasonable risk" has a meaning independent from a "significant risk." The plain meaning of a "significant risk" is a great danger. "Unreasonable risk" is a distinct term and requires more than evaluation of the significance of risk. "A risk could be significant but reasonable if the benefits were great enough to outweigh the risks." 69 Fed. Reg. at 6823. In other words, an "unreasonable risk" is relative to the circumstances; the potential risk is more "unreasonable" if the potential benefit is smaller. See Castrignano v. E.R. Squibb & Sons, Inc., 900 F.2d 455, 459 (1st Cir. 1990) (upholding jury instructions which define "unreasonable" as the "balance between the expected beneficial effects of the [product] as opposed to its harmful effects, if any."). The district court erred by conflating the terms "significant" and "unreasonable," thereby rendering "unreasonable" superfluous. In contrast to "significant risk," "unreasonable risk" accounts for whether the benefits justify the risks. The use of "unreasonable" to qualify risk in addition to "significant" makes it clear that Congress intended to integrate a risk-benefit analysis in the former. Thus, because we find the statute is clear, we now review the FDA's absolute prohibition of EDS under the APA.

"Conditions of Use"

Under DSHEA, the government bears the burden of proof to show that, "under conditions of use recommended or suggested in labeling," a dietary supplement is adulterated. 21 U.S.C. § 342(f)(1)(A)(i). It is undisputed that the FDA must consider the dosage recommended in a dietary supplement's labeling when making an adulteration determination under section 342(f)(1)(A). The district court held that the FDA failed "to prove by a preponderance of the evidence that a dosage of 10 mg or less of ephedrine alkaloids presents a significant or unreasonable risk of illness or injury, [and] has failed to give effect to the dose-specific language of [] § 342(f)(1)(A)(I)." 364 F. Supp. 2d at 1321.

In determining that EDS pose an "unreasonable risk of illness or injury," the FDA found that the weight loss and other health benefits possible from the use of EDS were dwarfed by the potential long-term harm to the user's cardiovascular system. The agency went on to enact a complete ban on the product after making a finding that any amount of EDS had negative ramifications on the cardiovascular system and, based on the FDA's analysis, EDS provided no benefits so great as to justify such risk.

The preponderance of the evidence standard[6] requires the party with the burden of proof to support its position with the greater weight of the evidence.

[6] Congress did not prescribe the quantum of proof required under DSHEA. Accordingly, the standard traditionally applied in administrative cases, the preponderance of the evidence standard, governs. See Steadman v. SEC, 450 U.S. 91, 95, 102 (1981).

See Metropolitan Stevedore Co. v. Rambo, 521 U.S. 121, 137-38 n.9 (1997) (explaining that the preponderance of the evidence standard "simply requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence . . . .") (citation omitted); Vesper Const. Co., Inc. v. Rain for Rent, Inc., 602 F.2d 238, 242 (10th Cir. 1979) ("by the greater weight of the evidence or, as it is sometimes called, the preponderance of the evidence."). The evidence relied on by the FDA to enact its ban of EDS covers over seven years of agency review, public notice and comment, peer-reviewed literature, and scientific data. It is the purview of the FDA to weigh the evidence, including the evidence submitted by Nutraceutical and other manufacturers during public notice and comment.

It is noteworthy that Nutraceutical relies on the 1999 GAO report to support its contention that the Final Rule lacks support. However, the GAO has since updated its findings and arrived at conclusions in support of the Final Rule. See GAO, Dietary Supplements: Review of Health-Related Call Records for Users of Metabolife 356 (GAO-03-494) (2003). Based on scientific data and AERs, the GAO concluded that EDS pose a significant risk of cardiovascular and nervous system effects among consumers who are young to middle-aged. See GAO, Dietary Supplements Containing Ephedra, Testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives (July 23, 2003); 69 Fed. Reg. at 6818 (GAO found that AERs

"were consistent with . . . the scientifically documented pharmacological and physiological effects of ephedrine alkoids.").

The FDA hired Dr. Inchiosa to study the effects of EDS on human health in 1999. Dr. Inchiosa used principles of pharmacokinetics[7] to examine the effects of ingestion of EDS on the human cardiovascular system. Dr. Inchiosa found that ephedrine would be expected to produce the same adverse cardiovascular effects (increased heart rate and blood pressure) as a comparable dose of the pharmacologically-related drug, epinephrine,[8] and that, consequently, no dose of ephedrine can be considered safe. Nutraceutical raises objections to Dr.

[7] A pharmacokinetic analysis is one which examines the bodily absorption, distribution, metabolism, and excretion of drugs. Merriam Webster's Collegiate Dictionary 871 (10th ed.1994).

[8] To reach his conclusions, Dr. Inchiosa relied on a peer-reviewed study of the effect of epinephrine in humans. William E. Clutter, et al., Epinephrine Plasma Metabolic Clearance Rates and Physiologic Thresholds for Metabolic and Hemodynamic Actions in Man, 66 J. Clin. Invest. 94 (July 1980). The Clutter study revealed significant increases in heart rate and blood pressure from epinephrine infusion at the rate of 0.5 µg/minute.

Inchiosa's study and methodology which it did not raise during the rulemaking.[9] Nutraceutical argues that Dr. Inchiosa's work is irrelevant to the effect of its low-level dosage EDS product because his study examined the impact of continuous injection of epinephrine into the bloodstream rather than ingestion of pills containing 10 mg or less of EDS.[10] The district court rejected the "mathematical model used [by Dr. Inchiosa] to compare doses of epinephrine to ephedrine." 364

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[9] Although Nutraceutical did not specifically object to Dr. Inchiosa's study and methodology during rulemaking, it did not thereby waive its objection. In a review of the decision of an administrative agency, a party waives its right to appeal an issue if it fails to object through comments or documents in the record. New Mexico Environmental Imp. Div. v. Thomas, 789 F.2d 825, 835 (10th Cir. 1986) (when agency solicited comments on the very issue being challenged, party "was obligated to make its record before the agency."); American Frozen Food Institute v. Train, 539 F.2d 107, 134 (D.C. Cir. 1976) ("What the industry failed to present to the Administrator during rulemaking procedures when specifically asked to comment cannot now be urged [as] a basis for invalidation [of the rule]."); see also Fuel Safe Washington v. F.E.R.C., 389 F.3d 1313 (10th Cir. 2004); Kennecott Copper Corp. V. E.P.A., 612 F.2d 1232, 1245 (10th Cir. 1979) ("it is well settled that industry must first utilize the opportunity for comment [on an agency regulation] before it may raise issues on appeal."). While Nutraceutical did not object to Dr. Inchiosa's study on the record, it did advance dissatisfaction with the scientific evidence relied on by the FDA during the rulemaking. Appellee's App., at 159-60 ("Nutraceutical submits these comments to show that there is absolutely no basis for concluding that [] whole-herb ephedra supplement products present a significant or unreasonable risk . . . ."). The FDA solicited comments on "new scientific evidence . . . concerning health risks associated with the use of dietary supplements containing ephedrine alkaloids." 68 Fed. Reg. 10417 (March 5, 2003). Dr. Inchiosa's study was not among the evidence referenced in the FDA's March notice. Id. Given that the FDA did not specifically ask for comments on Dr. Inchiosa's study and Nutraceutical did object to the new scientific evidence generally, it is appropriate for us to consider Nutraceutical's objections to Dr. Inchiosa's study in particular.

[10] Nutraceutical's conclusory allegation that there is insufficient science to support the FDA's conclusion that increased heart rate and blood pressure correlate to increased risk of cardiovascular disease is contrary to the vast scientific evidence in the administrative record.

F. Supp. 2d at 1315. To account for the different potency levels of ephinephrine and ephedrine, Dr. Inchiosa factored the greater potency of ephinephrine into his calculations. Dr. Inchiosa's work indicates that he exaggerated margins of error in order to come to a conservative conclusion that the cardiovascular effects produced by a dose of 9 mg of EDS daily may be dangerous.

Further, the FDA did not rely on Dr. Inchiosa's work alone.[11] The FDA's

[11] The FDA relied on multiple studies which demonstrated that EDS raise blood pressure and increase heart rate. The agency considered evidence from the well-known, scientifically established pharmacology of ephedrine alkaloids; peer-reviewed scientific literature on the effects of ephedrine alkaloids; and AERs of occurrences following consumption of EDS. 69 Fed. Reg. 6788. In its call for comments, the FDA specifically cited to the following peer-reviewed studies: Stephen Bent, et al., The Relative Safety of Ephedra Compared with Other Herbal Products, 138 Ann. Intern. Med. 468-72 (March 2003) (finding that EDS accounted for 64% of all adverse reactions to herbs in the United States, despite representing only 0.82% of herbal product sales); Paul G. Shekelle, et al., U.S. Dep't of Health & Human Servs., Agency for Healthcare Research & Quality, Assessment No. 76, Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects (Feb. 2003) (concluding that the use of ephedrine and/or the use of ephedra or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations); Lewis B. Morgenstern, et al., Use of Ephedra-Containing Products and Risk for Hemorrhagic Stroke, 60 J. Neurology 132-35 (2003) (concluding that ephedra is not associated with increased risk for hemorrhagic stroke, expect possibly at higher doses); David Samenuk, et al., Adverse Cardiovascular Events Temporally Associated With ma huang, an Herbal Source of Ephedrine, 77 Mayo Clinic Proceedings 12 (2002) (concluding that ephedra use is temporally related to stroke, myocardial infarction, and sudden death; underlying heart or vascular disease is not a prerequisite for ephedra-related adverse events; and the cardiovascular toxic effects associated with ephedra were not limited to massive doses); Christine Haller, et al., Pharmacology of Ephedra Alkaloids and Caffeine After Single-dose Dietary Supplement Use, 71 Clinical Pharmacology and Therapeutics 421-32 (June 2002) (after assessing the pharmokinetic effects of a single dose of EDS plus caffeine in eight healthy adults and finding that the mean heart rate response reached a maximum change of 15 beats/minute above the baseline, the authors concluded that dietary supplements that contain ephedra and caffeine can produce significant cardiovascular responses after a single dose); C. Boozer, et. al. Herbal Ephedra/Caffeine for Weight Loss: a 6-month Randomized Safety and Efficacy Trial, 26 Int'l J. Obesity Related and Metabolic Disorders 593-604 (2002) (concluding that dietary supplements that contain ephedra and caffeine promote weight and fat loss without the expected decrease in blood pressure); C. Boozer, et al., An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: A Randomized, Double-blind Trial, 25 Int'l J. Obesity and Related Metabolic Disorders, 316-24 (2001) (concluding that dietary supplements that contain ephedra and caffeine promote short-term weight and fat loss, but that safety with long-term use requires further investigation). The FDA also relied on an

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investigation also considered the findings of the National Institutes of Health, the GAO, and the 1996 Food Advisory Committee, among others. See also 364 F. Supp. 2d at 1320-21 ("Dr. Inchiosa . . . states that he cannot determine a safe level of EDS intake. This sentiment is echoed throughout the transcript of the [1996 Food Advisory Committee]. Several of the meeting's attendees made comments that a safe level could not be determined. There was, apparently, not enough evidence to support the conclusion that there is a safe level of intake for EDS."). The review of scientific literature is properly in the province of the FDA, to which this Court grants deference based on its expertise. See Weinberger v. Bentex Pharms., Inc., 412 U.S. 645, 653-54 (1973) (The FDA is "peculiarly suited" to evaluate conflicting scientific reports, a matter "not . . . well left to a court without chemical or medical background," because it "necessarily implicates complex chemical and pharmacological considerations.").

The majority of data in the administrative record suggests that EDS pose an unreasonable threat to the public's health. The FDA:

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[11](...continued)
investigation by the GAO which withdrew its earlier criticism of the FDA's 1997 proposed regulation of EDS after linking EDS use with heart attacks, strokes, seizures, death, and cardiac arrest. In addition, Dr. Inchiosa's study discussed the relationship between EDS and epinephrine in a transparent manner. Ephedrine alkaloids are members of a family of pharmacological compounds called sympathomimetics, which mimic the effects of epinephrine in the human body. 69 Fed. Reg. at 6789. Dr. Inchiosa extrapolated data on epinephrine to draw conclusions about EDS, but he did so using peer-reviewed data and generally accepted principles of pharmacology.

> looked at the seriousness of the risks and the quality and persuasiveness of the totality of the evidence to support the presence of those risks. [It] then weighed the risks against the importance of the benefits and the quality and persuasiveness of the totality of the evidence to support the existence of those benefits . . . giv[ing] more weight to benefits that improve health outcomes, especially in the long term, than to benefits that are temporary or rely on subjective measures such as feeling or looking better.

69 Fed. Reg. at 6799. The agency expressed that it would not deem EDS adulterated based on "risks that are insignificant and reasonable in light of the benefits from the supplement . . . ." Id. at 6825. The evidence in the administrative record was sufficiently probative to demonstrate by a preponderance of the evidence that EDS at any dose level pose an unreasonable risk. The greater weight of the evidence supports the FDA's ban on EDS, thus satisfying the agency's burden.

The FDA's extensive research identified the dose level at which ephedrine alkaloids present unreasonable risk of illness or injury to be so minuscule that no amount of EDS is reasonably safe. The FDA reasonably concluded that there is no recommended dose of EDS that does not present an unreasonable risk. Id. at 6829 ("dose limitations cannot change the unfavorable risk-benefit ratio of [EDS]"). The FDA was not arbitrary or capricious in its Final Rule; the FDA met its statutory burden of justifying a total ban of EDS by a preponderance of the evidence.

We find that the FDA correctly followed the congressional directive to analyze the risks and benefits of EDS in determining that there is no dosage level of EDS acceptable for the market. Summary judgment for plaintiffs was therefore improper, and summary judgment for defendants should have been entered. Accordingly, the district court's decision is reversed, and we remand for entry of judgment in favor of defendants. As noted above, Nutraceutical's Motion to Correct Oral Argument Record is granted.

REVERSED AND REMANDED.