No. 06-922

In the Supreme Court of the United States

NUTRACEUTICAL CORPORATION, ET AL., PETITIONERS

v.

ANDREW VON ESCHENBACH, COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

BRIEF FOR THE RESPONDENTS IN OPPOSITION

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QUESTIONS PRESENTED

In the Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, § 4, 108 Stat. 4328, Congress authorized the Food and Drug Administration (FDA) to remove dietary supplements from the market when they present "a significant or unreasonable risk of illness or injury" under the recommended conditions of use or, if no conditions of use are recommended, under ordinary conditions of use. 21 U.S.C. 342(f)(1)(A). Pursuant to that authority and FDA's rulemaking authority, 21 U.S.C. 371(a), FDA banned dietary supplements containing ephedrine alkaloids (EDS) at all dosage levels. The questions presented are:

1. Whether FDA properly interpreted the statute to require a risk-benefit analysis in determining whether a dietary supplement presents an unreasonable risk of illness or injury.

2. Whether the record compiled by FDA supports its determination that EDS at all dosage levels, including a recommended daily dose of 10 mg or less, present an unreasonable risk of illness or injury.

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OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1-21) is reported at 459 F.3d 1033. The opinion of the district court (Pet. App. 22-43) is reported at 364 F. Supp. 2d 1310.

JURISDICTION

The judgment of the court of appeals was entered on August 17, 2006. A petition for rehearing was denied on October 16, 2006 (Pet. App. 44-45). The petition for a writ of certiorari was filed on January 3, 2007. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

1. In 1994, Congress amended the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 301 *et seq.*, with the enactment of the Dietary Supplement Health and Education Act (DSHEA), Pub. L. No. 103-417, 108 Stat. 4325. Dietary supplements are generally regulated as foods under the FDCA, as amended by DSHEA. See 21 U.S.C. 321(ff). As a food, a dietary supplement may not be marketed if it is adulterated. 21 U.S.C. 331(a), (b), (c) and (k). Under a provision applicable only to dietary supplements, a dietary supplement is adulterated if it "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)(A). Congress directed "swift action" to be taken against dietary supplements "that are unsafe or adulterated." DSHEA § 2(13), 108 Stat. 4326.

2. Ephedrine alkaloids are members of a family of pharmacological compounds called sympathomimetics, which mimic the effects of epinephrine in the human body. Pet. App. 52. Dietary supplements containing ephedrine alkaloids (EDS) have been widely sold in the United States. *Id.* at 54. In the 1980s and 1990s, manufacturers promoted the sale of EDS for weight loss and enhancement of athletic performance. *Id* at 55. In the 1990s, the Food and Drug Administration (FDA) received numerous adverse event reports (AERs) relating to EDS. *Ibid.* Those AERs reported serious side effects associated with EDS use, including heart attacks, strokes, and death. *Ibid.*

In 1997, FDA proposed a regulation that involved warning labels and dosage restrictions. Pet. App. 55. The General Accounting Office issued a report urging further investigation. *Id.* at 58. In response, FDA withdrew a part of its proposed regulation. *Id.* at 58-59.

FDA continued to receive AERs concerning EDS use. Pet. App. 6. It also received numerous public comments on its proposed regulation. *Ibid.* Ultimately, the administrative record contained approximately 19,000 AERs and more than 48,000 comments. *Ibid.* FDA also had before it multiple studies and peer-reviewed scientific literature bearing on the effects of EDS. *Id.* at 17 n.11. Petitioner Nutraceutical Corporation made several submissions arguing that low-dosage EDS do not pose an unreasonable risk of injury or illness and therefore should remain on the market. *Id.* at 6.

In response to those submissions and others, FDA commissioned a study by Dr. Mario A. Inchiosa. Pet. App. 6. In his analysis, Dr. Inchiosa examined a peer-reviewed study showing significant increases in heart rate and blood pressure from epinephrine infusion at low levels. *Id.* at 16 n.8. Based on peer-reviewed studies, Dr. Inchiosa also concluded that ephedrine taken orally can be compared to epinephrine administered intravenously. In particular, those studies show that ephedrine is completely absorbed after oral administration, just as a drug that is delivered intravenously into the bloodstream is completely available to body tissue. C.A. App. 240. Based on generally accepted principles of pharmacology, Dr. Inchiosa then extrapolated from the data on epinephrine to reach conclusions about low-dose EDS. *Id.* at 19 n.11. To account for their different potency levels, Dr. Inchiosa factored the greater potency of epinephrine into his calculations. *Id.* at 17. Dr. Inchiosa

also exaggerated margins of error to make sure that the conclusions he reached on the danger level of EDS would be conservative ones. *Ibid.* Using that approach, Dr. Inchiosa concluded that a dose of 9 mg per day of EDS may be dangerous, and that no dose could be considered safe. *Id.* at 16-17.

3. After the conclusion of a seven-year investigation, FDA issued a final rule that banned EDS at all dosage levels. Pet. App. 6. FDA adopted that rule based on its assessment that EDS pose an "unreasonable risk" of illness or injury at all dose levels. *Id.* at 50. FDA concluded that an assessment whether a dietary supplement poses an "unreasonable risk" requires a risk-benefit analysis. *Id.* at 51. Applying that analysis, FDA concluded from multiple studies and the well-known pharmacology of ephedrine alkaloids that EDS raise blood pressure and increase heart rate, exposing users to risks of stroke, heart attack, and death. *Id.* at 51-52. FDA further concluded that EDS do not "provide a health benefit sufficient to outweigh these risks." *Ibid.* FDA explained that the best evidence for a benefit is for weight loss, but that evidence "supports only a modest short-term weight loss, insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese." *Ibid.* Based on Dr. Inchiosa's analysis and other evidence, FDA concluded that even low-dose EDS present an unreasonable risk of illness or injury. *Id.* at 99-101.

4. Petitioners filed suit in federal district court, seeking a declaration that FDA's final rule is invalid. Pet. App. 7. On cross-motions for summary judgment, the district court ruled in petitioner's favor. *Id.* at 22-43.

The court first held that FDA had erred in applying a risk-benefit analysis. Pet. App. 36-39. In the court's

view,"[t]he plain language of the DSHEA does not require a comparison of benefits and risks." *Id.* at 36. The court also concluded that a risk-benefit analysis improperly shifts the burden to EDS manufacturers to demonstrate a benefit. *Id.* at 38.

The district court next held that there was insufficient evidence to support FDA's across-the-board ban at all dose levels. Pet. App. 39-42. The court concluded that "[t]he plain language of the statute requires a dose-specific analysis," and, thus, "the proper focus here is on the evidence the FDA presented regarding the risks of low-dose EDS." *Id.* at 40-41. The court determined that Dr. Inchiosa's analysis was insufficient to support a finding that a dose of 10 mg per day presents an unreasonable risk, because his analysis was based on "a hypothetical mathematical model." *Id.* at 41. The court added that a "statement that a safe level cannot be determined" is not sufficient to meet the government's burden because the government must meet its burden through affirmative evidence rather than negative inference. *Id.* at 42.

5. The court of appeals reversed. Pet. App. 1-21. The court first held that "Congress unambiguously required the FDA to conduct a risk-benefit analysis under DSHEA." *Id.* at 10. The court reasoned that the term "unreasonable" necessarily connotes a comparison between the risks and benefits of a product. *Ibid.* The court rejected the district court's conclusion that a risk-benefit analysis improperly shifts the burden to the manufacturer to show the benefits of its product. *Id.* at 11. The court explained that, under a risk-benefit analysis, the burden is at all times on the agency to prove that the risks outweigh the benefits. *Id.* at 11-12.

The court of appeals next held that FDA had satisfied its burden of proving that EDS pose an unreasonable risk at daily doses of 10 mg or less. Pet. App. 14-20. The court explained that "[t]he 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." *Id.* at 20. The court added that "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." *Ibid.*

The court rejected petitioner's contention that Dr. Inchiosa's analysis did not support FDA's determination. The court emphasized that Dr. Inchiosa "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." Pet. App. 17. The court further explained that, while "Dr. Inchiosa extrapolated data on epinephrine to draw conclusions about EDS, * * * he did so using peer-reviewed data and generally accepted principles of pharmacology." *Id.* at 19 n.11.

ARGUMENT

The decision of the court of appeals is correct and does not conflict with any decision of this Court or any other court of appeals. Review by this Court is therefore not warranted.

1. Petitioners contend (Pet. 22-29) that the court of appeals erred in holding that DSHEA requires FDA to conduct a risk-benefit analysis in determining whether to ban a dietary supplement. That contention is without merit and does not warrant review.

DSHEA provides that a dietary supplement is adulterated if it "presents a significant *or* unreasonable risk of illness or injury." 21 U.S.C. 342(f)(1)(A) (emphasis added). Congress's use of the disjunctive "or" between the terms "significant" and "unreasonable" means that the statute contains two independent standards of risk—a "significant risk" and an "unreasonable risk." See *Reiter* v. *Sonotone Corp.*, 442 U.S. 330, 339 (1979) (statutory terms connected by a disjunctive should be given separate meanings, unless context dictates otherwise). While "significant" involves an evaluation of risk alone, in common usage, "unreasonable" is a comparative term that connotes a balancing of risks against benefits. 69 Fed. Reg. 6788, 6823 (2004). See *FDIC* v. *Meyer*, 510 U.S. 471, 476 (1994) (in the absence of prescribed definition, statutory terms should be construed in accordance with their ordinary meaning).

Indeed, in *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193, 203-204 (2005), this Court held that "unreasonable risk" in another provision of the FDCA contemplates a risk-benefit analysis. The provision discussed in *Merck* authorizes FDA to impose a "clinical hold" prohibiting the sponsor of a drug investigation from proceeding with the investigation if "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. 355(i)(3)(B)(i). Like the adulterated dietary supplement provision in DSHEA, 21 U.S.C. 342(f)(1)(A), the clinical hold provision does not require a risk-benefit analysis in express terms. The Court nonetheless held that a determination of "unreasonable risk" necessarily "involves a comparison of the risks and the benefits associated with the proposed clinical trials." *Merck*, 545 U.S. at 204.

Other FDCA provisions that require FDA to make an "unreasonable risk" determination, but do not define that term, likewise require a risk-benefit analysis. For example, under the FDCA, one characteristic of a Class III medical device is that it poses "a potential unreasonable risk of illness or injury." 21 U.S.C. 360c(a)(1)(C)(ii)(II). As the legislative history makes clear, a determination of unreasonable risk under that provision contemplates "a balancing of the possibility that illness or injury will occur against benefits from use." H.R. Rep. No. 853, 94th Cong., 2d Sess. 36 (1976). Another provision, 21 U.S.C. 360f(a), authorizes FDA to ban a medical device if it presents "an unreasonable and substantial risk of illness or injury." Although the FDCA does not specify how FDA should make that determination, an FDA implementing regulation states that the agency "will consider whether the * * * risk posed by the continued marketing of the device * * * is important, material, or significant in relation to the benefit to the public health from its continued marketing." 21 C.F.R. 895.21(a)(1). Because identical terms within the same statute generally "bear the same meaning," *Estate of Cowart* v. *Nicklos Drilling Co.*, 505 U.S. 469, 479 (1992), the "unreasonable risk" standard for determining whether a dietary supplement is adulterated likewise requires a risk-benefit balance.

Thus, the ordinary meaning of "unreasonable risk," the Court's decision in *Merck*, and the meaning of "unreasonable risk" in other provisions of the Act compel the conclusion that FDA is required to conduct a risk-benefit analysis. Even if the statute were ambiguous, however, those considerations would plainly be sufficient to render FDA's interpretation reasonable and there-

fore entitled to controlling weight under *Chevron U.S.A. Inc.* v. *NRDC*, 467 U.S. 837, 843-844 (1984).

Petitioners err in contending (Pet. 14-15) that use of a risk-benefit analysis effectively puts the burden of proof on a manufacturer to demonstrate that a dietary supplement is safe and effective and collapses the distinction between the FDCA's treatment of drugs and its treatment of dietary supplements. FDA expressly recognized that "Congress placed the burden on FDA to show 'unreasonable risk,'" Pet. App. 93, and it satisfied that burden by examining "the available scientific data and literature." *Id.* at 94. As the court of appeals concluded, "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." *Id.* at 11-12.

Thus, the court of appeals was clearly correct in holding that the statute requires a risk-benefit analysis. Nor is there any other basis for review of that issue. The court below is the first to address that issue. And far from presenting a recurring question, this is the first time that FDA has banned a dietary supplement from the market. This Court's review is therefore not warranted.

2. Petitioners contend (Pet. 16, 19-20) that FDA failed to comply with the statutory requirement to determine whether EDS pose an unreasonable risk at 10 mg per day, the amount recommended or suggested in their labeling. That contention is without merit and does not warrant review.

In its final rule, FDA stated that it had concluded that dietary supplements containing EDS "present an unreasonable risk of illness or injury under the condi-

tions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended, in labeling under ordinary conditions of use." Pet. App. 50. That conclusion embraces a determination that EDS pose an unreasonable risk of illness or injury at all doses recommended or suggested in labeling, including a recommended dose of 10 mg or less per day. As FDA explained, "we conclude, based on available science, that all dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury, regardless of how they are formulated or labeled, because the risks outweigh any benefits that may result from use of the products." *Id.* at 85-86. Indeed, FDA specifically addressed the possibility of permitting the marketing of low-dose EDS and rejected it because it concluded that low-dose EDS pose an unreasonable risk of injury or illness. *Id.* at 100-101.

Petitioners contend (Pet. 19) that there was insufficient evidence to support FDA's conclusion that a dose of 10 mg per day poses an unreasonable risk. That fact-bound contention does not warrant review. In any event, Dr. Inchiosa's study provided a sound basis for FDA's conclusion. Based on his study, Dr. Inchiosa concluded that a daily dose of only 9 mg of EDS would produce measurable increases in heart rate and systolic blood pressure and therefore may be dangerous. Pet. App. 16-17 & n.8.

Petitioners object (Pet. 16-17) to FDA's conclusion because it was not based on clinical trials of EDS taken at a dosage of 10 mg or less per day. But DSHEA does not prescribe or limit the kind of evidence on which FDA must rely in determining whether a dietary supplement poses an unreasonable risk. Because DSHEA does not require dietary supplement manufacturers to conduct

clinical trials on human subjects or to perform any testing and analysis of their products prior to marketing, FDA found "the available body of well-controlled clinical data [to be] limited." 69 Fed. Reg. at 6819. FDA also concluded that, given the numerous reports of serious adverse health effects (including death) that the agency had received even before it initiated the EDS rulemaking, it would be unethical and irresponsible for it to sponsor or encourage any clinical trials of actual EDS use. *Id.* at 6798, 6799.

Moreover, FDA's reliance on Dr. Inchiosa's study was appropriate. Because ephedrine and epinephrine are pharmacologically related and produce similar effects on the body, Dr. Inchiosa was able to draw a conclusion about the risks of low-dose EDS from data on the risk of a comparable dose of epinephrine. Pet. App. 16. FDA routinely considers the available information concerning pharmacologically related drugs when assessing a drug's safety before and after approval. 69 Fed. Reg. at 6799. It is no less reasonable for the agency to consider the available data on a pharmacologically related substance when determining whether a dietary supplement presents an unreasonable risk of illness or injury. *Ibid.*

Furthermore, as the court of appeals found, Dr. Inchiosa's calculations conservatively took into account the greater potency of epinephrine, and Dr. Inchiosa "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." Pet. App. 17. Dr. Inchiosa's analysis was also based on "peer-reviewed data, and generally accepted principles of pharmacology." *Id.* at 19 n.11. Thus, FDA based its determination that EDS present an unreason-

able risk at all dosage levels on the best available science. Cf. *Motor Vehicle Mfrs. Ass'n of the U.S., Inc.* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 52 (1983) ("It is not infrequent that the available data do not settle a regulatory issue, and the agency must then exercise its judgment in moving from the facts and probabilities on the record to a policy conclusion."); *Weinberger* v. *Bentex Pharms., Inc.*, 412 U.S. 645, 653-654 (1973) (FDA is "peculiarly suited" to evaluate evidence that "implicates complex chemical and pharmacological considerations.").

Petitioners contend (Pet. 19) that FDA improperly relied on the absence of evidence that there was a safe dose of EDS, rather than affirmative evidence that a daily dose of 10 mg or less would pose an unreasonable risk. In fact, however, FDA relied on both forms of evidence. Dr. Inchiosa's study supplied affirmative evidence that a daily dose of 9 mg of EDS would produce measurable increases in heart rate and systolic blood pressure and therefore could be dangerous. Pet. App. 16-17 & n.8. FDA also appropriately examined whether there was any evidence indicating that there was a safe level of EDS, and concluded that no such evidence could be found. *Id.* at 101. Because Dr. Inchiosa's study indicated that low-dose EDS pose an unreasonable risk, and no evidence indicated that there was a safe level of EDS, FDA soundly concluded that low-dose EDS pose an unreasonable risk.

Finally, petitioners contend (Pet. 17-18) that the court of appeals erred in failing to engage in de novo review of FDA's determination. In petitioners' view, de novo review is required by 21 U.S.C. 342(f), which provides that "[t]he court shall decide any issue under this paragraph on a de novo basis." As the court of appeals

explained, however, petitioners' action seeks "review" of an agency decision, and it therefore necessarily arises under the Administrative Procedure Act (APA), 5 U.S.C. 706. Pet. App. 8. The normal rules of judicial review of administrative action therefore apply.

Only one other court of appeals has addressed that issue, and it has reached the same conclusion. In *NVE Inc* v. *HHS*, 436 F.3d 182, 196 (2006), the Third Circuit held that "DSHEA's de novo standard is inapplicable in an APA challenge to administrative rulemaking, [and, therefore,] the normal rules for judicial deference regarding agency action apply" to the review of FDA's rule banning EDS.

Moreover, the court of appeals' decision upholding FDA's determination did not ultimately depend on its selection of the appropriate standard of review. The court of appeals concluded that "[t]he 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," and that "[t]he greater weight of the evidence supports the FDA's ban on EDS, thus satisfying the agency's burden." Pet. App. 20. In light of the evidence in the record, that conclusion is clearly correct. In any event, that fact-bound determination does not warrant review.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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