### Ephedra

#### I. Introduction

Ephedra, a medicinal herb also known as Ma Huang, has been used for thousands of years as a cure to the common cold, asthma, and other respiratory diseases and more recently in pharmacological products such as bronchodilators and decongestants. In the early 1990s, dietary supplement manufacturers began marketing weight loss supplements, energy boosters, and performance enhancers containing ephedra.

To regulate dietary supplements, including ephedra, Congress passed the Dietary Supplement Health and Education Act of 1994 (DSHEA) as an amendment to the Federal Food, Drug, and Cosmetic Act (FDCA), one of several statutes governing the Food and Drug Administration (FDA). The legislation established safety and other standards for dietary supplements, required nutrition and ingredient labeling, and created an Office of Dietary Supplements at the National Institutes of Health and a Commission on Dietary Supplement Labels.

The FDA first attempted to regulate dietary supplements under the DSHEA with a rulemaking concerning dietary supplements containing ephedra, which it subsequently withdrew in part. After several deaths and hundreds of adverse events allegedly resulted from dietary supplements containing ephedra, the FDA reopened the rulemaking and issued in 2004 a final rule banning all dietary supplements containing ephedra on the basis that they were “adulterated” as defined by the DSHEA. The FDA’s rulemaking was tested in several court cases and a petition for certiorari currently awaits review by the U.S. Supreme Court.

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6 See Section VI, infra.

Meanwhile, lawmakers passed the first major changes to dietary supplement law since the DSHEA.\(^8\) Signed into law on December 22, 2006, the Dietary Supplement and Nonprescription Drug Consumer Protection Act (the “Dietary Supplement Act”) amends Chapter VII of the FDCA by mandating serious adverse event reporting for dietary supplements and nonprescription drugs and provides for possible criminal sanctions against manufacturers.\(^9\)

II. The Food and Drug Administration

The FDA’s mission includes protecting and advancing the public health “by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.” The FDA is also charged with “helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.”\(^10\)

The FDA has been in existence for over 100 years under various departments: Agriculture; the former Department of Health, Education, and Welfare; and, presently, within the Department of Health and Human Services.\(^11\) In 1906, Congress passed the Food and Drugs Act, which prohibited the interstate transport of unlawful food and drugs under penalty of seizure or prosecution.\(^12\) Although this law focused on drug labeling and misbranding, as well as preventing or listing additives and ingredients, initial enforcement focused on adulterated food.\(^13\)

Responding to a tragedy of 100 toxic-substance related deaths, Congress passed the FDCA in 1938, increasing the FDA’s enforcement power, providing the FDA jurisdiction over previously unregulated cosmetics and devices, and instituting safety measures such as requiring instruction labels on drugs and a pre-market approval process for new drugs.\(^14\) The FDCA also prohibited “false therapeutic claims for drugs.”\(^15\) Since 1938, the law has been amended numerous times.\(^16\)

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\(^11\) History of the FDA, Origins, http://www.fda.gov/oc/history/historyoffda/default.htm. What is now known as the FDA was known before 1930 as the Division of Chemistry, the Bureau of Chemistry, and the Food, Drug, and Insecticide Administration. See id.


\(^14\) 21 U.S.C. § 301 et seq.; see also James T. O’Reilly, Food and Drug Administration, § 3.4 (2005).

\(^15\) See 21 U.S.C. § 301 et seq.; see also FDA’s Role in Protecting and Promoting Public Health, available at http://www.fda.gov/centennial/centennial_files/textonly/index.html. The U.S. Supreme Court ruled in 1911 that the 1906 Food and Drugs Act did not, contrary to its claims, prevent false therapeutic claims by drug manufacturers.
Under the FDCA, “drugs” fall into three categories or an inclusive fourth category comprised of articles intended to become a component of any of the other three categories. These three categories are (1) “articles recognized in the official United States Pharmacopoeia” or a similar standard-setting body for prescriptions and over-the-counter medications; (2) “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals”; and (3) “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”

When determining whether an article is a drug under the second or third categories, the agency looks to the vendor’s intent. However, even if a vendor does not intend to sell an item as a drug, the FDA can still govern it as a drug, which is a term that does not include food or dietary supplements. Dietary supplements are classified as “food” and may be regulated under the FDCA and subjected to the FDA’s rules on adulteration and misbranding.

III. The Dietary Supplement Health and Education Act (DSHEA)

Prior to 1994, the FDA regulated many dietary supplements by defining them as “food additives,” thus subjecting them to regulation—including pre-market approval—under the FDCA. Concerned that this “back door” regulation by the FDA improperly impeded public access to safe dietary supplements, Congress enacted the DSHEA in 1994. The Act amended the FDCA and placed the burden on the FDA to prove that the product is unsafe, or “adulterated,” and thus, subject to regulation.

Under the DSHEA, a dietary supplement is considered adulterated if it 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;


Amendments to the FDCA have included a broad range of topics such as food and color additives, animal drugs, drug abuse control, infant formula, saccharin labeling, orphan drugs, nutrition information and food allergen labeling, prescription drug marketing and importation, safe medical devices, and dietary supplements.


See O’Reilly, § 13.3. Sunscreen is one example of such a product. See id. § 13.3.

Foods are not subject to pre-market approval under the FDCA.


22 See 21 U.S.C. §§ 321(f), 331; 21 U.S.C. § 342(f) (“the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated.”); FDA, Center for Food Safety and Applied Nutrition, Dietary Supplements, Overview, http://www.cfsan.fda.gov/~dms/supplmnt.html. A key distinction is that the FDA can require premarket approval for drugs, food additives, and medical devices, but not for dietary supplements. 21 U.S.C. § 413. The DSHEA does not permit dietary supplements labels to claim that the product is intended for us in the mitigation, treatment or prevention of disease; labels suggesting such uses make the products subject to regulation as a drug.
(B) is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury;
(C) the Secretary declares to pose an imminent hazard to public health or safety . . . ; or
(D) contains a dietary ingredient that renders it adulterated . . . .

To facilitate the FDA’s monitoring of dietary supplements, the DSHEA established a system requiring dietary supplement manufacturers to report adverse events resulting from the use of their products.

IV. Adverse Event Reports and the FDA’s Response, 1993-1997

In 1993, the FDA began receiving adverse event reports (AERs) concerning dietary supplements containing naturally occurring ephedrine alkaloids, ephedra’s active ingredient, and documenting health problems ranging from insomnia and arrhythmia to heart attack, stroke, and, in a few cases, death. The AERs also revealed that many incidents involved otherwise healthy young adults not normally at high risk for cardiovascular problems.

In response to the growing number of AERs received, the FDA convened an ad hoc Working Group of its Food Advisory Committee (“Working Group”) to evaluate the safety of dietary supplements containing ephedrine alkaloids. Comprised of medical and scientific experts as well as industry and consumer representatives, the Working Group held a meeting on October 11-12, 1995, to review the evidence contained in the 325 AERs received and take public comments on the safety of ephedrine alkaloids. Ultimately, the Working Group recommended that the FDA: (1) establish dosage limits for ephedrine and ephedrine alkaloids, (2) require warning labels on product packaging, and (3) establish good manufacturing practices for products containing ephedrine and ephedrine alkaloids.

Following the Working Group’s meeting, the number of AERs received concerning dietary supplements containing ephedrine alkaloids nearly doubled. The agency became

26 At the time the Working Group convened in October 1995, the FDA had already received 325 AERs concerning dietary supplements containing ephedrine alkaloids. See 62 Fed. Reg. at 30680 (June 4, 1997).
27 Information on the FDA’s “Good Manufacturing Practice” regulations is available at http://www.fda.gov/cdrh/devadvice/32.html.
29 By June 1996, eight months after the Working Group meeting, the FDA had received almost 600 AERs, and by June 1997, it had received 200 more, totaling 800. See 62 Fed. Reg. at 30683.
increasingly concerned after it received reports about two young, otherwise healthy males whose deaths the medical examiner specifically attributed to the use of dietary supplements containing ephedrine alkaloids. 30 Given the escalation of occurrences and the increased severity of adverse events related to dietary supplements containing ephedrine alkaloids, the FDA convened a larger meeting of its Food Advisory Committee to study the problem in conjunction with the Working Group. 31

In preparation for the Food Advisory Committee meeting, the agency carefully examined and analyzed the approximately 600 AERs received about products containing ephedrine alkaloids. The FDA discovered that 92% of the adverse events related to products marketed as weight loss aids or energy supplements, 5% related to products touted as enhancing athletic performance, and the remaining products were sold as an alternative to illicit street drugs. 32 Given the marketed purposes of ephedrine alkaloid products, the FDA was not surprised to discover that 75% of the AERs concerned females—the segment of the population most likely to use weight loss and energy supplements. Of greater concern was that 56% of the adverse events, including heart attack and stroke, occurred with persons under the age of 40 and more than 80% concerned persons under the age of 50. 33 The AERs also revealed that adverse events from ephedrine alkaloid products were unpredictable in pattern and severity even when the products were used according to the package instructions or under ordinary use. 34

The Advisory Committee met on August 27-28, 1996, to review the Working Group’s findings and new evidence detailed in the AERs received since October 1995. A majority of the Advisory Committee recommended completely removing dietary supplements containing ephedrine alkaloids from the market, while other members suggested establishing guidelines for safer per-serving and daily use amounts. 35

By 1997, the FDA had received and reviewed over 800 AERs of adverse events directly attributable to ephedrine alkaloid products. 36 The Working Group concluded, and the Advisory Committee concurred, that sufficient evidence existed to establish that the use of dietary supplements containing ephedrine alkaloids may cause serious adverse events.

V. Regulatory Action


Determining that the use of ephedrine alkaloid supplements is a “serious and significant health concern,” the FDA chose to regulate ephedrine alkaloids through administrative

31 See id. at 30683.
32 See id. at 30684. Ephedrine is a component of illicit drugs such as ecstasy. See Sachs, p. 686.
34 See id. at 30684.
35 See id. at 30680.
36 See 62 id. at 30679, 30691.
rulemaking under the DSHEA rather than through “back door” enforcement actions brought under the FDCA. On June 4, 1997, the agency issued a Notice of Proposed Rulemaking (NPRM) addressing dosing, labeling, and warning statements of dietary supplements containing one or more ephedrine alkaloids and related alkaloids. Specifically, the NPRM proposed three ways that dietary supplements containing ephedrine alkaloids could be considered adulterated: (1) if the single-serving dosage exceeded 8 milligrams, (2) if the label recommended a single dose in excess of eight milligrams or a daily intake of more than 24 milligrams, or (3) if the supplement also contained a product with stimulant effects (such as caffeine). The NPRM further suggested that the product include a warning label stating that the product should not be used for more than seven days and is not intended for long-term use and that consuming more than the recommended dosage could lead to serious health effects, including heart attack, stroke, or death.

The FDA received a voluminous number of comments responding to its proposed rule, primarily from the dietary supplement industry and consumers. Opponents of the proposed rule argued that the AER data did not establish a causal connection to ephedrine alkaloids, that the dosage limitations were not based upon scientific evidence, and that the labeling requirements were excessive.

During the comment period, the Commission on Dietary Supplement Labels released its final report (“Commission Report”) on the regulation of label claims and statements for dietary supplements. The Commission Report recommended, inter alia, that the FDA take swift enforcement action to address the safety concerns regarding products containing ephedrine alkaloids.

In July 1999, the U.S. General Accounting Office (GAO)—pursuant to a request of the House Committee on Science made in September 1998—issued a report on the NPRM, concluding that, based on the evidence provided, ephedrine alkaloid-containing supplements can cause serious health problems and recommending further data collection and review. However,
the GAO report also criticized the FDA’s reliance on AERs as the basis for the proposed restrictions on dosage, frequency, and duration of use. Ultimately, the report cited a need for additional study and information and concluded that although the AERs signaled a serious health risk, the FDA had failed to establish the causal link between ephedrine alkaloids and the events contained in the reports.45

B. Partial Withdrawal, 2000

On April 3, 2000, the FDA withdrew substantial portions of the NPRM, including: the proposed finding that a dietary supplement is “adulterated” if it contains 8 mg or more of ephedrine alkaloids per serving or if the label recommends a daily intake of more than 24 mg; the proposed label statement restricting product usage to seven days; the proposed prohibition on labeling claims encouraging long-term intake; and the proposed warning that taking more than the recommended serving may cause heart attack, stroke, seizure, or death.46 The agency retained the NPRM’s provisions prohibiting the use of known stimulants in products containing ephedrine alkaloids and requiring that ephedrine supplements carry a statement warning against its use by people with certain diseases and medical conditions.47

The FDA simultaneously released information concerning an additional 270 cases of adverse events received by the FDA between February and September 1997 and another 140 AERs received prior to March 31, 1999.48 The FDA also announced its intention to participate in an August 2000 meeting convened by the U.S. Department of Health and Human Service’s Office of Women’s Health to discuss information about the safety of dietary supplements containing ephedrine alkaloids, take public testimony on ephedra use, and provide an opportunity to review the analysis of experts inside and outside the FDA.49 The meeting revealed differences in opinion between the FDA and outside experts and also identified several needs, including: a more reliable system for monitoring adverse events; adequate warning labels; consumer education; recognition of the role of ephedrine alkaloids when used to treat medical conditions, such as obesity; and long-term trials to establish dose levels and duration guidelines.50

Although the FDA withdrew a large portion of its proposed rule for further study, the medical community continued to warn the public about the health risks associated with ephedra and many states took action to regulate the dietary supplements. Due to the significance of ephedra’s adverse health effects, the New England Journal of Medicine released earlier than it

47 See id.; see also CRS Report, p. 4.
49 See CRS Report, p. 4.
50 See id., p. 5.
initially intended a study on the effects of dietary supplements with ephedra.\textsuperscript{51} Another study by the American Association of Poison Control Centers found that, based on sales and U.S. poison control center data, dietary supplements containing ephedra accounted for 64\% of adverse events from herbal products, even though ephedra dietary supplements comprised only 0.82\% of herbal products sold.\textsuperscript{52} As a result of these and other studies, and in the absence of FDA regulation, approximately half the States enacted legislation to regulate or ban products containing ephedrine alkaloids.\textsuperscript{53}

\textbf{C. Reopening the Rulemaking, 2003}

By the end of February 2003, the FDA had received over 1600 AERs associated with ephedra.\textsuperscript{54} Following the death of several athletes, including Baltimore Orioles pitcher Steve Bechler, the FDA made available new information about dietary supplements containing ephedrine alkaloids and reopened the NPRM comment period for an additional 30 days.\textsuperscript{55} The agency also sought comments on whether, in light of recent evidence, it “should determine that dietary supplements containing ephedrine alkaloids are adulterated because they present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or under ordinary conditions of use if the labeling is silent.”\textsuperscript{56}

The new information included a report by the Southern California Evidenced Based Practice Center (RAND) commissioned by the National Institutes of Health.\textsuperscript{57} RAND conducted an independent review of available evidence and scientific research on the risks and benefits of ephedra and ephedrine products. The report identified 21 “sentinel events” associated with ephedrine products, including stroke, heart attack, and death. Among the report’s findings, RAND concluded that short-term use of supplements containing ephedrine alkaloids and caffeine produced dramatic short-term weight loss results and that ephedrine alone has little bearing on athletic performance.\textsuperscript{58}

\begin{itemize}
  \item \textsuperscript{51} C.A. Haller and N.L. Benowitz, \textit{Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids}, NE J. Medicine, Nov. 6, 2000.
  \item \textsuperscript{53} See Sachs, at 685-87. Several countries such as Canada, Ireland, Germany, Jordan, and Saudi Arabia have also banned or restricted sales and importation of products containing ephedra. See id.
  \item \textsuperscript{56} 68 Fed. Reg. 10417 (Mar. 5, 2003).
  \item \textsuperscript{58} See n.57, supra.
\end{itemize}
On December 30, 2003, the FDA issued a press release announcing that it planned to prohibit the sale of dietary supplements containing ephedra, warning consumers of the health risks associated with ephedrine alkaloids, and urging them to stop using dietary supplements containing ephedra immediately. The FDA also sent a letter to 60 dietary supplement manufacturers, stating that the FDA was preparing to issue a final rule banning products containing ephedrine alkaloids and warning them of possible enforcement actions if the manufacturers failed to comply with the final rule.

D. The Final Rule, 2004

On February 11, 2004, the FDA published its final rule deeming botanical ephedra “adulterated” and banning from the marketplace all dietary supplements containing ephedrine alkaloids, since “dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) (21 U.S.C. 342(f)(1)(A)) of the [Federal Food, Drugs, and Cosmetics] act because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use.” The ephedra ban marked the first time the FDA exercised its authority under the DSHEA to remove a supplement ingredient from the marketplace based upon its “unreasonable risk” to consumers.

In interpreting the DSHEA, the FDA adopted a risk-benefit balancing test as the appropriate standard for evaluating whether the risk was unreasonable. This standard, as explained in the final rule, requires a “relative weighing of the product’s known and reasonably likely risks against its known and reasonably likely benefits.” The final rule banning ephedra became effective on April 12, 2004.

VI. Court Cases

Ephedrine alkaloids manufacturers subsequently challenged the final rule in the federal courts. The first case, NVE Inc. v. Dept. of Health and Human Services., resulted in an interlocutory appeal to the U.S. Court of Appeals for the Third Circuit, which decided in favor of


61 The DSHEA only regulates naturally occurring, or botanical, ephedra, whereas the FDCA more strictly regulates the synthetic form of ephedra, which is not the subject of controversy.

62 Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (Feb. 11, 2004). The FDA could also have explored whether it had the legal authority to remove dietary supplements from the market under the “imminent hazard to public health or safety” standard. However, the FDA noted that it was “confident that it has a clear legal basis for taking effective action to protect consumers under the ‘unreasonable risk’ standard” and that it did “not believe that it is necessary to look to other authorities” to take action banning dietary supplements containing ephedra. See FDA, Questions and Answers About FDA’s Actions on Dietary Supplements Containing Ephedrine Alkaloids (Feb. 6, 2004).

the FDA and remanded the proceeding to the U.S. District Court for the District of New Jersey, which has yet to see any further action. In the second case, a Utah federal judge limited the FDA’s ability to enforce a ban against the selling of ephedra products as dietary supplements, temporarily preventing the agency from taking action against Nutraceutical Corporation, a Utah-based company that sued to block the ban. The FDA appealed the decision to the U.S. Court of Appeals for the Tenth Circuit, which reversed, upholding the FDA’s ability to enforce a ban against the selling of ephedra products as dietary supplements.

A. **NVE Inc. v. Dept. of Health and Human Services**

NVE Pharmaceuticals Inc. (NVE), the New Jersey-based manufacturer and distributor of ephedrine alkaloid products, including Stacker 2, brought suit in March 2004 seeking to set aside the regulation, claiming that FDA violated the Administrative Procedure Act (APA). NVE alleged that the FDA violated its right to due process under the Fifth Amendment by failing to give NVE a reasonable opportunity to comment on the substance of the rule. NVE also sought to supplement the administrative record, contending that the district court must decide the issues NVE raised on a “de novo basis” in accordance with the DSHEA, as codified at 21 U.S.C. § 342(f)(1). In orders dated August 4, 2004 and August 12, 2004, the district court declined NVE’s request, limiting its review to the 133,000-page administrative record for the challenged rule.

Pursuant to 28 U.S.C. § 1292(b), the district court certified those orders for interlocutory appeal and identified questions for review. The U.S. Court of Appeals for the Third Circuit denied NVE’s interlocutory appeal, stating that under the APA a court may only conduct a trial de novo of an administrative adjudication that is “unwarranted by the facts.” The case at bar, found the Third Circuit, was a rulemaking, not an adjudication. Further, according to the Third Circuit, Congress intended de novo review under the DSHEA to apply only when a court is deciding whether a dietary supplement qualifies as an adulterated food. More specifically, the court found that, under the DSHEA, application of the de novo provision is limited to judicial inquiries aimed at establishing the presence or absence of one of the conditions under which a dietary supplement may be deemed adulterated. According to the Third Circuit, “In the instant case, the District Court must not consider whether the FDA’s determination that [ephedrine alkaloids] is adulterated was correct, but rather if its action in rulemaking was arbitrary,

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64 The DSHEA does not provide a private cause of action, nor does it contain a waiver of sovereign immunity that would permit NVE to sue a federal agency. NVE Inc. v. Dep’t. of Health & Human Svcs., No. 04-cv-999, p. 7 (D.NJ Aug. 4, 2004).

65 See id. at 2-4; 21 U.S.C. § 342(f)(1) (“In any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis.”).


67 NVE Inc. v. Dep’t. of Health & Human Svcs., 436 F.3d 182, 189 (3d Cir. 2006).

68 See id. at 189-190, 191.
capricious, contrary to law, in excess of the FDA’s statutory jurisdiction, or preceded by inadequate notice.”

Further evidence that Congress did not intend anything otherwise, the Circuit Court found, included the DHSEA provision requiring that those proceedings requiring de novo review also require that the United States bear the burden of proof, thus limiting the de novo standard to judicial reviews of enforcement actions brought by the government, not challenges independently initiated by affected parties.

NVE claimed that the de novo provision also authorizes discovery to determine what evidence the FDA considered in reaching its decision and whether the administrative record is complete. The right to conduct discovery, however, derives not from the DSHEA, said the Third Circuit, but from the APA, which only permits discovery in cases involving alleged agency bias and in cases with an administrative record lacking fundamental documents or otherwise incomplete on its face, neither of which NVE had alleged in the instant case.

In its order, the district court ruled that the FDA’s factual determinations and legal conclusions are not entitled to deference in the instant suit. Although not identified by the district court as a question for review, the Circuit Court addressed that issue suo sponte as permitted by 28 U.S.C. § 1292(b). Acknowledging that the courts owe deference to an agency’s interpretation of the statute and regulations it administers, per the Chevron doctrine, the Third Circuit stated, “Because DSHEA’s de novo standard is inapplicable in an APA challenge to administrative rulemaking, the normal rules for judicial deference regarding agency action apply in the instant suit. We therefore disagree with this aspect of the District Court’s ruling.” The Third Circuit remanded the case in March 2006 to the district court for further proceedings. The district court has yet to see any further action on the case, presumably because NVE filed for bankruptcy on August 10, 2005, in the U.S. Bankruptcy Court for the District of

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69 Id. at 191.
70 See id. at 191-92.
71 See id. at 182, 195-196.
73 See 436 F.3d at 196 (citing Howard Hess Dental Labs. Inc. v. Dentsply Int’l, Inc., 424 F.3d 363, 368 (3d Cir. 2005)); see also, Yamaha Motor Corp., U.S.A. v. Calhoun, 516 U.S. 199, 205 (1996) (“any issue fairly included within the certified order because it is the order that is appealable, and not the controlling question[s] identified by the [D]istrict [C]ourt.”) (emphasis in original); 16 Charles Alan Wright et al., Federal Practice and Procedure § 3929, p. 388 (2d ed. 1996) (“The court may . . . consider any question reasonably bound up with the certified order, whether it is antecedent to, broader or narrower than, or different from the question specified by the district court.”).
75 436 F.3d at 196 (citing United States v. Mead Corporation, 533 U.S. 218, 226-27 (2001) (holding that administrative implementation of a particular statutory provision qualifies for Chevron deference when Congress delegated authority to agency ‘to make rules carrying the force of law’); Sw Pa. Growth Alliance v. Browner, 121 F.3d 106, 117 (3d Cir. 1997) (“A reviewing court ‘must generally be at its most deferential’ when reviewing factual determinations within an agency’s area of special expertise.”) (quoting New York v. EPA, 852 F.2d 574, 580 (D.C. Cir.1988)).
New Jersey. Meanwhile, it remains a defendant in approximately 117 personal injury, product liability, and wrongful death cases.

**B. Nutraceutical Corp. v. Von Eschenbach**

Dietary supplement manufacturers Nutraceutical Corporation and its brand Solaray® also brought action against the FDA’s final rule banning ephedrine alkaloids, alleging that it violates the FDCA, as amended by the DSHEA, through an improper determination of adulteration under 21 U.S.C. § 342(f), and that it also violates the APA. In *Nutraceutical Corp. v. Von Eschenbach*, 364 F.Supp.2d 1310 (D.Utah 2005), the United States District Court for the District of Utah granted summary judgment in favor of manufacturers, enjoining the ban and remanding the rulemaking to the FDA. According to the court, the FDA’s risk-benefit analysis supporting the ban was contrary to Congress’ intent and the FDA failed to prove by a preponderance of the evidence that ephedrine alkaloids pose an unreasonable risk of illness or injury at 10 mg. or less a day.

The FDA appealed to the Tenth Circuit, which reversed the district court’s decision. As an initial matter, the Tenth Circuit concluded, like the Third Circuit in *NVE Inc. v. Dept. of Health and Human Services*, that the proceeding is not subject to de novo review under the DSHEA, since it is not an enforcement proceeding, and that the agency should be afforded controlling weight under the *Chevron* doctrine, unless the final rule was arbitrary, capricious, or manifestly contrary to the statute.

In *Nutraceutical Corp.*, however, the Tenth Circuit reversed the district court after finding that “Congress unambiguously required the FDA to conduct a risk-benefit analysis under DSHEA.” Under the statutory definition of “adulterated”—meaning to “present a significant or unreasonable risk of illness or injury”—the Tenth Circuit agreed with the FDA that “[t]he plain meaning of ‘unreasonable’ ... [is to] connote [ ] comparison of the risks and benefits of the product.” The Tenth Circuit further found that the analysis was performed properly, as the FDA maintained the burden of proving that ephedrine alkaloids are adulterated.

In its August 17, 2006, decision, the Tenth Circuit also reviewed the administrative record and concluded that the evidence therein was “sufficiently probative to demonstrate by a preponderance of the evidence that [ephedrine alkaloids] at any dose level pose an unreasonable risk. The greater weight of the evidence supports the FDA’s ban on [ephedrine alkaloids], thus

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76 *NVE, Inc.*, Bankruptcy Petition No. 05-35692-NLW (Bankr. D. NJ).


79 *Nutraceutical Corp. v. Von Eschenbach*, 439 F.3d 1033, 1037-1038 (10th Cir. 2006).

80 *Id.* at 1038.

81 *Id.* (quoting 21 U.S.C. § 342(f)(1); 69 Fed.Reg. 6788, 6823 (2004)).

82 439 F.3d at 1039.
After the Tenth Circuit issued its decision, Nutraceutical filed a motion in the district court to renew the two remaining causes of action not previously ruled upon on in its case. According to Nutraceutical, the court did not rule on its APA claims arising from the disparate treatment of ephedrine alkaloid containing conventional foods and ephedrine alkaloid containing dietary supplements under the Final Rule and that the Final Rule adopted a legislative “risk-benefit” standard without advance notice and opportunity for comment. Nutraceutical later filed a motion for summary judgment on these two issues and the government filed a cross motion. Meanwhile, Nutraceutical Corp. filed a petition for certiorari with the Supreme Court on January 3, 2007. The district court judge did not stay the proceeding and scheduled oral briefing on the matter for March 21, 2007.

C. Civil Actions

In an order issued on April 13, 2004, the Judicial Panel on Multidistrict Litigation consolidated in the U.S. District Court for the Southern District of New York 15 personal injury and wrongful death actions from 10 jurisdictions against at least 24 dietary supplement manufacturers. According to the Panel, the actions involved common questions of fact, including the alleged side effects of ephedra-containing products and whether defendants knew of these side effects and either concealed, misrepresented or failed to warn of them. The Panel also centralized the actions to “serve the convenience of the parties and witnesses and promote the just and efficient conduct of this litigation.” Since then, some parties have settled and some of the subordinate proceedings have been dismissed.

In the existing consolidated proceeding, *Parks v. Herbalife Int’l of Am., Inc.*, the district court issued an order on December 13, 2006, excluding in part the testimony of a plaintiff’s case-specific cardiology expert and of three defendants’ experts and excluding in its entirety the testimony of the plaintiff’s internist-pharmacology expert. The remaining parties subsequently filed cross motions for summary judgment on January 18, 2007.

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83 Id. at 1040.
84 Plaintiff’s Motion for Renewal and Supporting Memorandum, Nutraceutical Corp. v. Von Eschenbach, filed Nov. 8, 2006 (D.Utah) (No. 2:04cv00409).
85 Plaintiff’s Motion for Summary Judgment and Supporting Memorandum, Nutraceutical Corp. v. Crawford, filed Dec. 20, 2006 (D.Utah) (No. 2:04cv00409). While maintaining the same docket number, the case’s name in the district court was changed without notice or explanation in December 2006 from *Nutraceutical Corp. v. Von Eschenbach* to *Nutraceutical Corp. v. Crawford*.
88 Id.
VII. Enforcement Mechanisms

The FDA’s final rule on ephedra marked “the first time U.S. officials have blocked the sale of an over-the-counter nutritional supplement that poses a ‘significant and unreasonable risk’ under the conditions of use on the label or as commonly consumed.” In addition to the FDA’s usual enforcement tools, including seizures, injunctions, and in limited situations, recalls and civil penalties, the DSHEA provided the FDA with the new authority to stop the sale of a dietary supplement that poses an “imminent hazard” by engaging in formal rulemaking. The FDA also utilizes advisory and warning letters and guidance to obtain compliance with the FDCA/DSHEA and its regulations. This section will briefly discuss each of these enforcement tools.

A. “Imminent Hazard” Authority

The DSHEA authorizes the FDA to immediately stop shipment of any dietary supplement product that poses “an imminent hazard to public health or safety.” If the Secretary declares a dietary supplement or dietary ingredient “to pose an imminent hazard,” the government must promptly conduct an administrative proceeding under sections 554 and 556 of the APA, during which, “FDA must review the merits of the ‘imminent hazard’ conclusion, and the product cannot be sold to the public.”

With the DSHEA, the FDA has more power with its “imminent hazard” authority to immediately stop the marketing of a dietary supplement than it has for any conventional food regulated under the FDCA. On the other hand, the DSHEA places certain limitations on the FDA’s enforcement authority. For instance, when the FDA decides to enforce its “imminent hazard” authority against a dietary supplement manufacturer, prior to the reporting of any violation to a United States Attorney, the FDA must give the manufacturer ten days notice and the opportunity to present its views. This mandatory provision was intended to “foreclose the FDA from exercising the discretion that allows the agency to forego such a hearing prior to reporting a criminal violation. The goal was to mandate one last chance to talk prior to a civil proceeding.”

B. Seizures

91 21 U.S.C. §342(f)(1)(C). The FDA only has recall and civil penalty authority in limited situations.
92 Id.
93 Id.
95 See id.
Section 304 of the FDCA authorizes seizures that are “often an expeditious means of removing adulterated dietary supplements from the marketplace.”\(^9\) When determining whether to seize adulterated or misbranded dietary supplements, “FDA considers prior warnings, the significance of the violation, current status of the manufacturer, pending and adjudicated seizure actions, the public health risk, and the amount of the product to be seized.”\(^9\) Some posit that, “because seizures are less resource-intensive for the FDA than injunctions, which must be monitored, mass seizure can be a very effective tool in light of resources expended and compliance achieved.”\(^1\)

C. **Injunctions**

The FDA may enjoin a manufacturer from selling adulterated or misbranded dietary supplements under section 302 of the FDCA. The FDA may pursue an injunction when: “there is a current and definitive health hazard or a gross consumer deception that requires immediate action to stop the violative practice and prevent the same in the future; correction efforts, with notice, have failed, there are significant amounts of violative products owned by the same person in many locations, and multiple seizures are impractical or uneconomical; or there are chronic violative practices which do not amount to a health hazard or gross consumer fraud, but have not been corrected through voluntary or other regulatory approaches.”\(^1\)

D. **Recalls and Warnings**

Under the FDA’s regulations, adulterated or misbranded dietary supplements may also be subject to a recall, which is defined as “a firm’s removal or correction of a marketed product, including its labeling and/or promotional material, after the FDA determines the product is in violation of the laws it administers.”\(^1\) Recalls do not include a market withdrawal or a stock recovery.\(^1\)

As a matter of practice, the FDA provides advance warning of activities the FDA believes violates the FDCA, DSHEA or their concomitant regulations. Warnings can take many forms such as “a warning letter, an FDA administrative action, a list of observations provided by the investigator at the conclusion of an inspection, or meetings with management.”\(^1\)

E. **Guidance**


\(^9\) See Urban, 47 Food & Drug L.J. at 412.

\(^1\) Id. at 412.

\(^1\) Id. at 413.

\(^1\) Id. at 414.

\(^1\) 21 CFR Part 7 et. seq.

\(^1\) Urban supra, 47 Food & Drug L.J. at 415 (“Market withdrawals, in contrast to a recall, are a firm’s removal or correction of a distributed product, when the product involves either no violation or minor violations for which the FDA would not take action.”).

\(^1\) Id., at 412.
To secure compliance, the FDA issues various guidance documents. Specifically, the DSHEA amended the FDCA to authorize the FDA to issue regulations to “prescribe good manufacturing practices for dietary supplements.” On March 13, 2003, the FDA issued a notice of proposed rulemaking on good manufacturing practice requirements for dietary supplements and received over 1,600 pages of comments.

F. Future Use

Although the DSHEA provided the FDA a tool to assist in the immediate removal of dietary supplements that pose an “imminent hazard,” the DHSEA’s amendment of the FDCA did not modify the FDA’s existing authority to enjoin, seize, or recall adulterated or misbranded dietary supplements. Based on current practice, it appears that the FDA will continue, where applicable, to provide warnings to manufacturers and the public regarding adulterated or misbranded dietary supplements. Further, the FDA will undoubtedly continue to issue guidance on various matters as a means to inform the industry regarding good manufacturing practices and scientific surveys.

VIII. Looking Ahead: Future Regulation of Dietary Supplements

During and after the NPRM, only drug and biologic product manufacturers were legally required to file AERs with the FDA. On December 22, 2006, however Congress passed and the President signed into law the Dietary Supplement Act, which requires manufacturers, packers, and distributors of nonprescription drugs and dietary supplements to report serious adverse events to the FDA. The Dietary Supplement Act defines an adverse event as “any health-related event associated with the use of a nonprescription drug that is adverse,” including overdose, drug abuse, “failure of expected pharmalogical action,” “an event occurring from withdrawal,” and serious adverse events as those that result in death, life-threatening experiences, inpatient hospitalization, persistent or significant disability or incapacity, congenital anomaly, birth defect, and events requiring medical intervention. Consumers and health care workers can submit complaints or report concerns about food, drugs, biologic products, and dietary supplements to the FDA.

106 68 Fed. Reg. 12157-63 (Mar. 13, 2003). FDA also asked for comments on its draft guidance regarding the type and quality of evidence for “structure and function” claims. See 69 Fed. Reg. 64962-64 (Nov. 9, 2004) (acknowledging that 21 U.S.C. § 343(r)(6) requires that a dietary supplement manufacturer making a structure/function or general well-being claim have substantiation that the claim is truthful and not misleading).