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*Analyzing the Laws, Regulations, and Policies
Affecting FDA-Regulated Products*

The Food and Drug Administration's
Actions on Ephedra and Androstenedione:
Understanding Their Potential Impacts
on the Protections of the Dietary
Supplement Health and Education Act

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I. INTRODUCTION: SUMMARY OF THE PROBLEM

The Food and Drug Administration (FDA) will interpret new law over time in a way that gives more authority to the agency and less flexibility to industry. This obvious statement, generally applicable to most federal agencies, bears repeating in light of FDA's ephedra final rule¹ and FDA's recent warning letters declaring that androstenedione (andro) is an illegally marketed "new dietary ingredient" (NDI).² Both FDA actions are examples of the agency's willingness to apply new legal interpretations to solve existing regulatory "problems," and both actions have important implications for the entire dietary supplement industry.

The ephedra rule sets a new standard, a "risk/benefit" standard, for determining whether dietary supplements are "adulterated" pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA),³ as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA).⁴ As applied in the ephedra final rule, the risk/benefit standard appears to be at least as strict as the risk/benefit standard that FDA applies to drugs. Those who drafted DSHEA never intended the use of such a standard to regulate dietary supplements, and this standard is unauthorized by law. Further, the risk/benefit standard was established without proper notice-and-comment rulemaking and, therefore, without considered industry input. If FDA's risk/benefit standard survives ongoing legal challenges, this standard will lower the bar that FDA must meet to prove adulteration, with the result that FDA will challenge and ban more products on the basis of adulteration.

FDA's recent warning letters concerning andro raise two important issues. First, the letters show how the new risk/benefit standard announced in the ephedra rule could impact FDA's review of NDI notifications, further restricting market access. In addition, FDA's andro warning letters provide an early warning of their own that FDA may be creating a new "lawfully marketed" standard for pre-DSHEA "grandfather" status. FDA's "lawfully marketed" standard appears to require anyone relying on grandfather status for a dietary ingredient to prove the following: 1) that the ingredient was marketed prior to October 15, 1994, and 2) that such marketing was legal, meaning proof that the ingredient was generally recognized as safe (GRAS) and not an illegal "food additive" *before* 1994. This second prong of the test could prove to be an insurmountable hurdle for any ingredient that was not already affirmed as GRAS by FDA prior to 1994.

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¹ See Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (Feb. 11, 2004).

² Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Androstenedione Warning Letters, *available at* <http://www.cfsan.fda.gov/~dms/andrlist.html#letter> (last visited Jan. 13, 2005).

³ Pub. L. No. 75-717, § 402(f), 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 342(f)).

⁴ Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified in scattered sections of 21 U.S.C.).

Both the risk/benefit standard and FDA's NDI "lawfully marketed" standard raise serious concerns about the continued marketing of many supplements that are widely sold and popular with consumers, but are not traditional vitamins and minerals. What should be clear to industry is that, if FDA is left to its own devices, the agency will find ways around the market protections afforded by DSHEA. FDA's willingness to reinterpret the law to provide unauthorized powers to the agency, and the consequences of failing to resist this tendency, are better understood in light of FDA's past attempts to regulate evening primrose oil (EPO), black currant oil (BCO), and other popular and safe dietary supplements as illegal "food additives."

II. A BRIEF HISTORY OF FDA'S DEALINGS WITH SUPPLEMENTS PRE-DSHEA

FDA interpreted the FDCA in the 1980s and early 1990s as requiring FDA premarket approval of a food additive petition for virtually all dietary ingredients other than traditional vitamins and minerals. FDA effectively blocked market access for nontraditional dietary supplements by refusing to approve dietary supplement food additive petitions and by initiating seizure actions against products that did not fit FDA's "traditional" mold.

In the process of enforcement, FDA made arguments that were irrational from both a legal and scientific perspective. Two products, EPO and BCO—both marketed as sources of a beneficial fatty acid, gamma-linolenic acid (GLA)—became the focus of litigation over the application of the food additive provisions to dietary supplements. In the end, FDA's misuse of the food additive requirements to restrict the supplement market to traditional vitamins and minerals led to the passage of DSHEA.

A. *The EPO Litigation*

In 1985, FDA issued an Import Alert for EPO,⁵ which instructed FDA officials to detain EPO labeled for food use because the agency considered it an unsafe food additive.⁶ In 1988, Efamol, a dietary supplement manufacturer based in the United Kingdom, initiated discussions with FDA regarding the procedure for obtaining FDA affirmation, through the existing petition process, of the status of EPO as GRAS. Before a GRAS affirmation petition was filed, however, FDA initiated two seizure actions of Efamol's EPO products alleging, among other things, that EPO was not GRAS and was, therefore, an unapproved food additive.⁷

In this litigation, FDA argued in part that EPO could not be GRAS because EPO might cause cancer, birth defects, hydrocephalus in newborns, convulsions, immunosuppressions, and excessive bleeding, and that it also was unsafe because it contained pesticides and toxic oxidative byproducts.⁸ FDA made these arguments even though supplements containing EPO were then (and are now) widely sold internationally and on the U.S. market, with virtually no reports or other evidence of adverse effects and with no renewed claims of FDA concern post-DSHEA.

⁵ See FDA, Import Alert No. 66-04: Oil of Evening Primrose (1985).

⁶ Pursuant to 21 U.S.C. § 321(s), a substance is a "food additive" if 1) the intended use of the substance may reasonably be expected to result in its becoming a component of any food, and 2) the substance is not generally recognized by qualified experts as safe (GRAS) under the conditions of its intended use. A "food additive" is deemed to be adulterated unless FDA has issued a regulation permitting its use. 21 U.S.C. §§ 342, 348, respectively.

⁷ See *United States v. 45/194 kg. Drums of Pure Vegetable Oil*, No. CV 89-73, 1989 WL 248572 (C.D. Cal. Nov. 30, 1989), *aff'd*, 961 F.2d 808 (9th Cir. 1992); *United States v. 21 Drums of Food and Drug*, 761 F. Supp. 180 (D. Me. 1988).

⁸ See *45/194 kg. Drums of Pure Vegetable Oil* (C.D. Cal 1989) (FDA Expert Declarations).

The Ninth Circuit upheld a district court ruling that EPO was not GRAS, illustrating the difficulty that the GRAS standard posed for even the safest dietary supplements pre-DSHEA.⁹ Demonstrating the resources that FDA was willing to expend to keep the dietary supplement market free from nontraditional products like EPO, soon after the Ninth Circuit issued its ruling, FDA awarded the Commissioner's Special Citation to sixty-one FDA personnel, who comprised the "Evening Primrose Oil Litigation Team."¹⁰

B. *The BCO Litigation*

FDA's two seizure actions against BCO products involved dietary supplement products consisting of pure oil extracted from black currant seeds.¹¹ FDA alleged in both cases that BCO was not GRAS and was, therefore, an unapproved food additive. The initial issue for the courts in the BCO case, however, was whether BCO was a pure, single ingredient food that FDA was not authorized to regulate under the FDCA "food additive" provisions. If the "food additive" provisions were not implicated, then whether BCO was GRAS was irrelevant.

FDA argued that the addition of BCO to a gelatin capsule caused the BCO to become a "food additive" within the meaning of the FDCA, and that as a "food additive," the substance could not be marketed as a dietary supplement without first applying for and obtaining FDA approval of a "food additive" petition.¹² The U.S. Court of Appeals for the Seventh Circuit, in a unanimous three-judge opinion, stated as follows:

The only justification for this Alice-in-Wonderland approach [i.e., FDA's "food additive" allegation] is to allow the FDA to make an end-run around the statutory scheme [W]e hold that [BCO] encapsulated with glycerin and gelatin is not a food additive FDA has not shown that [BCO] is adulterated or unsafe in any way.¹³

The U.S. Court of Appeals for the First Circuit, also in a unanimous three-judge opinion, ruled similarly to the Seventh Circuit:

FDA's reading of the [FDC] Act is nonsensical The proposition that placing a single-ingredient food product into an inert capsule as a convenient method of ingestion converts that food into a food additive perverts the statutory text, undermines legislative intent, and defenestrates common sense. We cannot accept such anfractuous reasoning.¹⁴

Congress concluded that unless it stepped in and passed DSHEA, FDA would continue to try to prohibit the marketing of safe and proper dietary supplements through illegal means:

⁹ See *45/194 kg. Drums of Pure Vegetable Oil*, 961 F.2d at 808.

¹⁰ *Dietary Supplements: Hearings Before the House Comm. on Appropriations, Subcomm. on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies*, 103d Cong. 208 (1993).

¹¹ *United States v. Two Plastic Drums . . . Viponte Ltd. Black Currant Oil*, 984 F.2d 814 (7th Cir. 1993); *United States v. 29 Cartons of . . . an Article of Food*, 987 F.2d 33 (1st Cir. 1993). The product at issue in the EPO litigation was EPO to which vitamin E had been or was to be added as a preservative. The Ninth Circuit distinguished the EPO cases from the BCO cases on this basis. See *45/194 kg. Drums of Pure Vegetable Oil*, 961 F.2d at 808.

¹² See *Two Plastic Drums*, 984 F.2d at 816; *29 Cartons of . . . an Article of Food*, 987 F.2d at 36.

¹³ *Two Plastic Drums*, 984 F.2d at 819-20.

¹⁴ *29 Cartons of . . . an Article of Food*, 987 F.2d at 37, 39.

Although a fair reading of the current statute [i.e., the “food additive” provisions of the FDCA], as most recently interpreted by two United States courts of appeal, should make . . . amendment [of the FDCA by DSHEA] unnecessary, the committee has heard testimony that the FDA has rejected these [judicial] holdings. The committee is therefore concerned that the FDA will persist in such litigation, and thereby continue to subject small manufacturers to the choice of abandoning production and sale of lawful products, or accepting the significant financial burden of defending themselves against baseless lawsuits [brought by the FDA].¹⁵

The sentiment expressed in this Senate Report, and the extreme hostility that FDA’s overreaching caused among consumers, led to the passage of DSHEA by unanimous votes in both the House and the Senate.

C. *The Dietary Supplement Health and Education Act*

Through DSHEA, Congress sought to open the market to safe dietary supplements and to protect these products from future FDA efforts to keep safe products from the market through several key amendments to the FDCA, including the following:

- (1) DSHEA amended the FDCA definition of “food additive” to exempt dietary supplements from this definition;¹⁶
- (2) DSHEA defined the term “dietary supplement” very broadly to include not only vitamins and minerals, but also ingredients that FDA had in the past kept off the market, including herbs and any “dietary substance” that might be used to “supplement the diet by increasing the total dietary intake;”¹⁷ and
- (3) DSHEA added a new section to the food adulteration provisions of the FDCA establishing a unique standard for dietary supplement safety—“significant or unreasonable risk of illness or injury under . . . conditions of use recommended or suggested in labeling”—and clarified that FDA, not industry, bore the burden of proof on adulteration in any enforcement action.¹⁸

DSHEA also added important provisions to the FDCA to augment FDA’s ability to ensure product safety, requiring that dietary supplements meet the requirements of current good manufacturing practice regulations (GMPs),¹⁹ authorizing the Department

¹⁵ S. REP. NO. 103-410, at 21 (1994).

¹⁶ See 21 U.S.C. § 321(s)(6).

¹⁷ *Id.* § 321(ff).

¹⁸ *Id.* § 342(f)(1). Clarification of the burden of proof issue might seem unnecessary because courts historically have held that FDA bears the burden of proof in any seizure actions on the issue of adulteration. Further, FDA’s General Counsel and Commissioner had testified in Congress when the “food additive” provisions were added to the FDCA that FDA bore the burden of proof on lack of GRAS status in enforcement proceedings. See *Federal Food, Drug, and Cosmetic Act (Chemical Additives in Food): Hearings Before a Subcomm. on Interstate and Foreign Commerce*, 84th Cong. 226 (1956); *Food Additives: Hearings Before a Subcomm. on Interstate and Foreign Commerce*, 84th Cong. 455 (1958). Nonetheless, FDA repeatedly argued in court that industry bore the burden of proof on GRAS issues. This FDA tactic was eliminated by specifying in 21 U.S.C. § 342(f)(1) that FDA bears this burden of proof.

¹⁹ 21 U.S.C. § 342(g)(1). Contrary to repeated assertions in the press, it is not true that there are no GMP requirements for dietary supplements. The GMP regulations that apply to food products, 21 C.F.R. pt. 110, also apply to dietary supplements. FDA has done almost nothing to enforce these requirements, and has taken too long to issue more specific regulations for dietary supplements, as FDA is authorized to do pursuant to 21 U.S.C. § 342(g)(2).

of Health and Human Services (DHHS) to order the immediate removal of any product presenting an imminent hazard,²⁰ and requiring that industry notify FDA of the scientific basis for safety for certain new dietary ingredients.²¹ Through DSHEA, Congress struck a careful balance between permitting greater access to the market for safe supplements that FDA previously had kept off the market, and providing FDA with the additional authority the agency needed to protect the public health from unsafe products.²²

For the first ten years after DSHEA, industry's main concern has been FDA's lack of enforcement of the regulations that apply to dietary supplements, which has led to repeated but untrue stories in the press that dietary supplements are unregulated and to general public concern over product quality and safety. Through the ephedra rule, the developing NDI policies, and the impending GMP regulations, FDA is taking the first real steps to implement and enforce DSHEA's provisions.

Industry and its trade associations need to carefully evaluate these actions to assess how they impact the market protections that Congress provided in DSHEA. Unfortunately, FDA's first efforts indicate that the agency's old assumptions that nontraditional supplements are unsafe and that speculative safety concerns are a sufficient basis for removing products from the market have not changed. If industry fails to recognize these signals, the protections afforded by DSHEA easily could be lost.

III. HOW FDA'S EPHEDRA RULE AND ANDRO LETTERS UNDERCUT DSHEA

Industry generally has welcomed the departure of what arguably are the two most controversial dietary supplement ingredients—ephedra and andro. It is not the loss of these ingredients *per se* that is harmful to the protections gained under DSHEA. The problem lies with the new legal theories that FDA has adopted to enable the agency to remove these ingredients, and the long-term implications of these new interpretations, which are applicable—and presumably will be applied—to the entire industry.

A. FDA's Ephedra Rule

FDA's ephedra rule creates a number of important problems for industry, including: 1) a new "risk/benefit" standard for assessing adulteration that is unauthorized by law and was developed without notice-and-comment rulemaking; 2) a new adulteration standard that significantly lowers FDA's burden of proof, making it easier for FDA to argue that products containing nontraditional dietary ingredients are adulterated; and 3) a standard for weight-loss benefits that requires long-term clinical studies that the supplement industry generally cannot afford to conduct.²³

When considering the impact of FDA's statements in the ephedra rule, it is essential to remember that any FDA statements of policy or interpretation published in the *Federal Register* represent an "advisory opinion" of the agency, "unless subsequently repudiated by the agency or overruled by a court."²⁴ An FDA advisory opinion "repre-

²⁰ *Id.* § 342(f)(1)(C).

²¹ *Id.* § 350b.

²² For a detailed discussion of all of the regulatory and enforcement tools at FDA's disposal, see Stephen H. McNamara & A. Wes Siegner, Jr., *FDA Has Substantial and Sufficient Authority to Regulate Dietary Supplements*, 57 *FOOD & DRUG L.J.* 15 (2002).

²³ See 69 *Fed. Reg.* at 6788. FDA's ephedra rule raises other significant problems, including FDA's finding that the law does not permit synthetic equivalents of dietary ingredients. *Id.* at 6793 (col. 2). The Coalition to Preserve DSHEA has filed a citizen petition with FDA objecting to FDA's policy on synthetic equivalents. See Citizen Petition, Coalition to Preserve DSHEA, FDA Dkt. No. 2004-0169 (Apr. 8, 2004).

²⁴ 21 C.F.R. § 10.85(d).

sents the formal position of FDA on a matter and [except in unusual situations involving immediate and significant danger to health] obligates the agency to follow it until it is amended or revoked."²⁵

FDA has announced in the ephedra rule that the agency will use a risk/benefit standard to evaluate dietary supplements under the "unreasonable risk" standard set by 21 U.S.C. § 342(f)(1).²⁶ The legality of FDA's new risk/benefit standard has been challenged in a lawsuit.²⁷ The major legal issues that this standard raises are summarized below.

A dietary supplement is regulated as a food under chapter IV of the FDCA. There is *no* provision in the regulatory framework of chapter IV for FDA to identify, quantify, assess, or take any action based on the benefits of any type of food. Rather, chapter IV limits FDA to regulating foods for safety and food labeling for full and truthful disclosure. Consistent with this limitation, DSHEA added section 413 to chapter IV of the FDCA, and established a standard of FDA review for NDIs; FDA must determine, based on the information supplied in the notification, whether the NDI "will reasonably be expected to be safe."²⁸ Therefore, section 402(f)(1)(A), interpreted in the context of chapter IV, similarly limits FDA to considering only the safety risks of a dietary supplement without regard to its benefits.

In its ephedra rule, FDA asserts "[t]he plain meaning of 'unreasonable' ... connotes comparison of the risks and benefits of the product."²⁹ This assertion is illogical on its face. The only comparison connoted by "unreasonable" is between itself and "reasonable." Deciding whether a "risk of illness or injury" from a food is "reasonable" or "unreasonable" may include a variety of factors, but there is nothing inherent in the concept of "reasonable" that requires one of those factors to be the benefits of a food. On the contrary, the overall scheme of chapter IV, in which food safety determinations never include consideration of the benefits of a food, makes it clear that FDA cannot determine that a dietary supplement poses an "unreasonable risk" based on a risk/benefit calculation.

FDA's view that "unreasonable risk" always implies a risk/benefit comparison is refuted by evidence in another part of the food chapter of the FDCA. FDCA section 408(l)(5)³⁰ provides that a food containing certain pesticide residues may not be deemed unsafe unless it poses "an unreasonable dietary risk." Consistent with chapter IV's other food safety provisions, benefits from the contaminated food are not considered in making this determination—in direct contradiction of FDA's interpretation of "unreasonable risk" in section 402(f)(1)(A).

Relying on the medical device provisions in FDCA chapter V as support for a risk/benefit interpretation of "unreasonable risk" in section 402(f)(1)(A), FDA undercuts its own argument.³¹ In chapter V, balancing the risks and benefits of medical devices is *explicitly* required for safety and effectiveness determinations, which must include "weighing any probable benefit to health ... against any probable risk of injury or illness."³²

It is a fundamental canon of statutory construction that "[w]here Congress includes particular language in one section of a statute but omits it in another section of the same

²⁵ *Id.* § 10.85(e), (f).

²⁶ FDA did not address the issue of whether ephedra products present a "significant" risk under section 342(f)(1), and therefore the meaning that FDA might ascribe to this separate prong of the adulteration analysis for dietary supplements is unknown. 69 Fed. Reg. at 6793-94.

²⁷ *Nutraceutical Corp. v. Crawford*, No. 2:04CV00409 (D. Utah filed May 3, 2004).

²⁸ 21 U.S.C. § 350b(a)(2).

²⁹ 69 Fed. Reg. at 6823 (col. 1).

³⁰ 21 U.S.C. § 346a(l)(5).

³¹ 69 Fed. Reg. at 6823 (col. 2).

³² 21 U.S.C. § 360c(a)(2)(C).

Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.³³ Further, the Supreme Court has noted that an “agency rule would be arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider.”³⁴

The Supreme Court has twice struck down agency rules when the agency improperly relied on a cost/benefit analysis in public health and safety matters. In *American Textile Manufacturers Institute, Inc. v. Donovan*,³⁵ the Court held that the word “feasible” did not permit an agency to apply a cost/benefit analysis. The Court distinguished the statute from statutes where Congress, in legislative history, directed a generalized balancing of costs and benefits.³⁶ No such legislative history exists with regard to section 402(f)(1)(A).

More recently, in *Whitman v. American Trucking Association*,³⁷ in an opinion authored by Justice Scalia, the Court interpreted whether the Clean Air Act permitted the Environmental Protection Agency (EPA) to consider costs in setting standards. The statutory language authorized the EPA to set a clean air standard as necessary to protect the public health with “an adequate margin of safety.” The Court contrasted that statutory provision with other environmental statutes where Congress implicitly permitted or required economic costs to be considered. Justice Scalia concluded that “[w]e have therefore refused to find implicit in ambiguous sections of the [Clean Air Act] an authorization to consider costs that has elsewhere, and so often, been expressly granted.”³⁸ “Congress, we have held, 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.”³⁹

FDA’s new risk/benefit standard is flawed for at least one other reason. Assuming that statutory authority exists, the standard for declaring a dietary supplement to be adulterated that FDA has applied to ephedra is not based on language that the agency earlier proposed, but, instead, was announced only when it issued the ephedra rule. Indeed, no one reasonably would have expected that FDA would adopt the standard included in the ephedra rule in determining whether a dietary supplement presents an “unreasonable risk of illness or injury.” Because the standard contained in the ephedra rule is so dramatically different from that contained in the proposal, FDA deprived the public of the opportunity to comment on this provision, in violation of the Administrative Procedure Act.⁴⁰

In issuing the Final Rule, FDA incorrectly stated that its June 1997 proposed rule and the March 5, 2003 *Federal Register* notice⁴¹ “provided a sufficient basis to allow the public to anticipate our actions in this final rule.”⁴² When a final rule contains significant changes from a proposed regulation subject to notice-and-comment rulemaking, the revisions in the regulation are permitted only where the final rule is a “logical outgrowth” of the proposed rule.⁴³ Courts, in *American Water Works* and other cases, have

³³ *Russello v. United States*, 464 U.S. 16, 23 (1983).

³⁴ *Motor Vehicles Mfrs. Ass’n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

³⁵ 452 U.S. 490, 508-13 (1981).

³⁶ *American Textile Mfrs.*, 452 U.S. at 510 n.30.

³⁷ 531 U.S. 457 (2001).

³⁸ *Am. Trucking Ass’n*, 531 U.S. at 467.

³⁹ *Id.* at 468.

⁴⁰ 5 U.S.C. § 553(b), (c).

⁴¹ Dietary Supplements Containing Ephedrine Alkaloids; Reopening of the Comment Period, 68 Fed. Reg. 10,417 (Mar. 5, 2003).

⁴² 69 Fed. Reg. at 6797.

⁴³ *Am. Water Works Ass’n v. E.P.A.*, 40 F.3d 1266, 1274 (D.C. Cir. 1994).

not hesitated to set aside rules where the “interested parties could not reasonably have ‘anticipated the final rulemaking from the draft [rule].”⁴⁴ Indeed, in a case cited by FDA, the D.C. Circuit held that a portion of the rule would be invalidated because there was “too tenuous” a connection between the language in the proposed rule and the provision in the final rule.⁴⁵ Here, FDA never indicated before issuing the Final Rule that it was contemplating a risk/benefit analysis. Employing that analysis for dietary supplements is therefore illegal.

In sum, there is nothing in the FDCA that would authorize FDA to use a risk/benefit standard to determine whether a dietary supplement is adulterated. Even assuming such statutory authority, FDA never provided notice before issuing the ephedra rule that it was contemplating a risk/benefit analysis. Employing that analysis for either ephedra or dietary supplements in general is therefore illegal.

The lack of proper notice-and-comment rulemaking has caused considerable uncertainty about the new risk/benefit standard and the implications for other dietary ingredients. It is clear from how FDA applied the new risk/benefit standard to ephedra that FDA has diminished what previously was thought to be a substantial burden of proof to show that a dietary supplement is adulterated under 21 U.S.C. § 342(f)(1).

For any ingredient that lacks a generally accepted benefit based on reliable clinical studies, the risk/benefit standard amounts to an absolute safety standard—any question concerning safety, even if raised by isolated adverse events, would appear to be sufficient proof for FDA to prevail under FDA’s new risk/benefit standard. According to FDA:

[t]he Government’s burden of proof for ‘unreasonable risk’ is met when a product’s risks outweigh its benefits in light of the claims and directions for use in the product’s labeling In the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable.⁴⁶

FDA adds that “isolated adverse events alone might not be expected to constitute substantiation of risk.”⁴⁷ The clear implication of this statement is that if, in FDA’s view, “sufficient” evidence of benefits does not exist, isolated reports of adverse events could be sufficient *on their own* to prove adulteration under the new risk/benefit standard.

FDA’s application of the risk/benefit standard to ephedra raises two additional concerns—1) that FDA is applying a “drug” standard to evaluate dietary supplement safety, and 2) that FDA has effectively closed the door to the lucrative weight-loss market. In an attempt to calm fears that FDA might apply a drug standard to dietary supplements, FDA stated in the ephedra rule that “the act creates different evidentiary standards for dietary supplements and drugs. Therefore, we are not applying the drug safety standard to dietary supplements.”⁴⁸ FDA’s own rationale for banning ephedra, however, proves that the agency did use a “drug” standard, and shows that FDA’s new risk/benefit standard is, at a minimum, as strict as the standard FDA applies for the approval of prescription drugs.

⁴⁴ *Id.* at 1275 (citing *Anne Arundel Co. v. E.P.A.*, 963 F.2d 412, 418 (D.C. Cir. 1992)).

⁴⁵ *Small Refiner Lead Phase-Down Task Force v. E.P.A.*, 705 F.2d 506, 549, 551 (D.C. Cir. 1983).

⁴⁶ 69 Fed. Reg. at 6788 (col. 3).

⁴⁷ *Id.*

⁴⁸ *Id.* at 6795 (col. 3).

The substantial quantity of data supporting the weight-loss claims for ephedra was sufficient to cause the Federal Trade Commission (FTC) to avoid challenging ephedra weight-loss claims for lack of adequate substantiation, even in the midst of the FTC's development of programs to target weight-loss products. The FTC challenged unconditional *safety* claims for ephedra,⁴⁹ but did not challenge the science supporting the standard weight-loss claims for ephedra that were made throughout the industry. A DHHS-funded report compiled by the RAND Corporation confirmed that the available clinical studies proved that ephedra causes short-term (up to six months) weight loss, while recommending that a longer-term study be conducted to confirm that ephedra could be used long-term to maintain weight loss.⁵⁰ Nonetheless, FDA dismissed all of the ephedra data as inadequate because, according to the agency, "[w]e have not found evidence that demonstrates long-term weight loss with [ephedra] products."⁵¹

In FDA's view, ephedra, which FDA concedes has been proven to produce significant weight loss in repeated clinical studies of up to six months,⁵² has absolutely no proven health benefits because of the lack of longer-term studies. FDA has this to say about clinical data showing that ephedra is proven to produce significant weight loss over a six-month period:

We also agree that this modest weight loss effect may be perceived as a benefit by consumers who seek to lose weight for nonhealth-related purposes (e.g., to look slimmer). We do not agree, however, that these studies demonstrate the long-term weight loss necessary to provide health benefits.⁵³

FDA relied on a 1996 draft guidance for evaluating weight-loss *drugs* to establish a minimum length of one year for clinical trials of *dietary supplements* for weight loss to prove any health benefit, and a preferred length of two years.⁵⁴ Therefore, applying FDA's new risk/benefit analysis, because the clinical studies for ephedra would not be acceptable for FDA to approve a weight-loss drug application for ephedra, there is *no* weight-loss health benefit from ephedra, and "the presence of even a relatively small risk of an important adverse health effect" is unreasonable under FDA's interpretation of section 342(f)(1).⁵⁵ Put simply, FDA used a "drug" standard to ban ephedra.

FDA's ephedra rule effectively closes the market for any dietary supplements for weight loss that do not have, at a minimum, one-year clinical trials to establish weight-loss benefits. This is true for two reasons. First, if weight-loss claims were made for any dietary supplement product without at least a one-year study, presumably FDA would view those claims as "false and misleading" under 21 U.S.C. § 343(a)(1), causing the product to be misbranded. Second, any dietary supplement claiming to cause weight loss that lacked clinical trials of one-year duration would be adulterated under the precedent set in the ephedra rule if, for example, FDA received adverse event reports to support agency concerns of "the presence of even a relatively small risk of an important adverse health effect."

In the end, we are left to wonder what FDA has created through its legal manipulations aimed at a ban on ephedra. The real benefit intended by DSHEA was greater

⁴⁹ See, e.g., *FTC v. MetRx USA, Inc.*, No. 8:99CV01407 (C.D. Cal. Nov. 24, 1999).

⁵⁰ See PAUL SHEKELLE ET AL., EFFICACY AND SAFETY OF EPHEDRA AND EPHEDRINE FOR WEIGHT LOSS AND ATHLETIC PERFORMANCE ENHANCEMENT: CLINICAL EFFICACY & SIDE EFFECTS (AHRQ Pub. No. 03-E022) (Feb. 2003).

⁵¹ 69 Fed. Reg. at 6819 (col. 1).

⁵² *Id.*

⁵³ *Id.*

⁵⁴ See *id.* at 6820-21 (discussing weight-loss study standards).

⁵⁵ *Id.* at 6788 (col. 3).

consumer access to dietary supplements. FDA has now created a standard that requires companies to *prove*, through studies that will be held to drug standards, that the products they market benefit public health. Otherwise, even the most speculative evidence of an important adverse health effect will be sufficient to satisfy FDA's burden of proof for adulteration. This is a standard that appears at least as strict, and possibly more difficult, than the GRAS standard that DSHEA was meant to supplant.

B. Impending Problems on the NDI Front

FDA's ephedra ban and the agency's separately-issued warning letters banning andro raise serious concerns that FDA intends to apply the "new dietary ingredient" (NDI) provisions of the FDCA to further limit market access. As with ephedra, industry should be careful to separate an event that the industry appears to generally support—the removal of the ingredient andro—from the policies that FDA has developed in parallel with that regulatory action.

DSHEA added a section to the FDCA that recognized the general safety of dietary ingredients on the market pre-DSHEA, and required industry to submit premarket notifications to FDA for certain "new dietary ingredients."⁵⁶ This section of the law specified that the safety standard for the review of NDI notifications is "that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe."⁵⁷ As previously stated, this is a safety standard—pure and simple.

One of the dangers posed by FDA's adoption of a risk/benefit standard for proving adulteration of dietary supplements under 21 U.S.C. § 342(f)(1) is that the agency will apply the same standard to NDI reviews. FDA will argue that it makes no sense to do otherwise—if Congress intended FDA to use a risk/benefit standard for adulteration (FDA's view), then it makes no sense to review NDIs under a pure safety standard if such ingredients would fail the tougher risk/benefit standard once on the market. FDA already has stated this proposition in the andro warning letters—FDA notes in these letters that, pursuant to 21 U.S.C. § 342(f)(1)(B), a new dietary ingredient is "adulterated" if "there is inadequate information to provide a reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury."⁵⁸

Therefore, if industry decides to accept FDA's risk/benefit standard in the context of the ephedra rule, industry also must prepare for FDA rejections of NDIs based on lack of proof of benefits. It appears that FDA already has rejected one NDI notification for this reason.

In a December 26, 2000 letter concerning FDA's NDI review for a dietary ingredient that is a variant of folic acid, FDA stated that, in the agency's opinion, the NDI notification failed to demonstrate that this ingredient would be "reasonably expected to be safe" under the intended conditions of use.⁵⁹ One of the bases for FDA's conclusion was the following:

[T]he studies were not designed to determine whether L-5-methyl-THF will support human fetal growth and development during pregnancy. The scien-

⁵⁶ See 21 U.S.C. § 350b.

⁵⁷ *Id.* § 350b(a)(2).

⁵⁸ See CFSAN, FDA, Sample Warning Letter on Androstenedione (Mar. 11, 2004), at <http://www.cfsan.fda.gov/~dms/andltr.html> (last viewed Nov. 1, 2004).

⁵⁹ Letter from Felicia B. Satchell, Director, Division of Standards & Labeling Regulations, FDA, to Najib Sehat, Merck KGaA 2 (Dec. 26, 2000), available at http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0087_01.pdf (last visited Jan. 13, 2005).

tific evidence in your submission is insufficient to establish that L-5-methyl-THF is safe for use during pregnancy as an alternative to folic acid.⁶⁰

In effect, FDA determined that the NDI notification not only needed to provide data supporting safety, the notification also needed to establish that the fetal growth benefits for the product as a replacement for folic acid were proven before FDA would file the NDI notification.⁶¹

The consequence of FDA's predicted merging of the risk/benefit standard into NDI reviews will be a considerably more difficult NDI review process, with fewer NDI notifications filed by FDA. This will put a serious damper on innovation in the dietary supplement market and decrease consumer access to safe and potentially beneficial new ingredients.

The potential problems that could be caused by FDA's application of the new risk/benefit standard to NDI reviews are exacerbated by another aspect of FDA's ongoing development of NDI policy—FDA's use of a "lawfully marketed" standard for the pre-DSHEA exemption from NDI notifications. Before DSHEA was enacted, FDA had pursued regulatory actions based on allegations of "unapproved food additive" status against many once-popular dietary supplement ingredients—including calcium acetate, orotate compounds such as magnesium orotate, evening primrose oil, black currant oil, borage seed oil, linseed/flaxseed oil, chlorella, lobelia, St. John's Wort, and coenzyme Q10. Industry has assumed for more than ten years that these ingredients are legally marketed dietary supplement ingredients that had been "grandfathered" by DSHEA pursuant to 21 U.S.C. § 350b(c), and that these ingredients were thus not subject to the FDCA's NDI notification provisions. FDA appears to be developing a policy that would render all of the above ingredients—as well as many other widely-marketed ingredients, including virtually all herbs and herbal extracts—illegal under DSHEA unless they are first reviewed by FDA under the NDI notification process.

The FDCA, as amended by DSHEA, defines the term "new dietary ingredient" to mean "a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994."⁶² In FDA's recently-issued andro letters, and in NDI correspondence relating to *stevia* and other NDIs, FDA has changed the statutory language—"marketed in the United States before October 15, 1994"—to "*lawfully* marketed in the United States before October 15, 1994."

FDA has made it clear, in correspondence concerning the herb *stevia*, that the agency added "lawfully" because FDA believes that any company wishing to avoid the statutory requirement for filing an NDI notification must prove that the ingredient in question was on the market before October 15, 1994, *and also must prove that the ingredient was GRAS when it was marketed.*⁶³ FDA's letter regarding *stevia* states that, because the company seeking to market *stevia* as a dietary ingredient had entered into a consent decree prohibiting the sale of the ingredient due to FDA allegations that the ingredient

⁶⁰ *Id.*

⁶¹ While it is important that any product claiming to be a folic acid substitute be shown to provide the very important fetal development benefits, it also is important to separate this issue from issues of "safety" under the NDI and adulteration provisions of the FDCA. Unsubstantiated claims of benefits are subject to legal action under the misbranding provisions of the FDCA. 21 U.S.C. § 343.

⁶² *Id.* § 350b(c).

⁶³ Letter from Linda S. Kahl, Ph.D., Acting Director, Division of Programs and Enforcement Policy, FDA, to W. Patrick Noonan, Sunrider Corp. (Aug. 16, 1995), available at <http://www.fda.gov/ohrms/dockets/dockets/95s0316/m000002.pdf> (last visited Jan. 13, 2005).

was *not* GRAS (and was, therefore, an unapproved “food additive”), the company could not show that *stevia* was lawfully marketed prior to October 15, 1994.⁶⁴

The practical effect of FDA’s “lawfully marketed” standard is that the only dietary ingredients that are protected from the “food additive” requirements of the FDCA under DSHEA are those that are legal NDIs—meaning NDIs that have been reviewed through NDI notifications under section 350b(a)(2), or NDIs that do not require such notification because they are “present in the food supply” under section 350b(a)(1). The illogic of this approach becomes apparent when one considers that it was, to a large extent, FDA’s illegal application of the FDCA’s “food additive” definition that led to DSHEA and the addition of the “new dietary ingredient” requirements. The enormous stake the industry has in dietary ingredients that would be rendered illegal and subject to NDI review (under the new risk/benefit standard) requires active and coordinated opposition to the “lawfully marketed” standard.

IV. CONCLUSION

FDA predictably is making very serious efforts to weaken or even dismantle some of the key provisions of DSHEA. FDA’s new risk/benefit standard imposes drug-like safety and efficacy requirements on dietary supplements that could lead to the same type of FDA control over dietary supplements that the agency accomplished through its misapplication of the food additive provisions pre-DSHEA. FDA’s reinterpretation of the law applying to NDIs is a further indication of the agency’s intent to circumvent DSHEA, and also creates potentially serious market access problems for industry.

The dietary supplement industry, burdened with too many trade associations operating with competing interests, has been slow to recognize the threat of FDA’s new policies, or to organize any opposition. By opening the door to overzealous regulation, a continuation of industry’s current complacency threatens the balances that DSHEA created to ensure consumer access to a wide range of beneficial and safe dietary supplement products.

⁶⁴ A company marketing a dietary supplement that contains an NDI that meets the “present in the food supply” requirements of 21 U.S.C. § 350b(a)(1) need not file a notification. FDA’s recent NDI correspondence, however, shows that the agency also has interpreted this requirement very narrowly, in order to increase the types of ingredients for which notification is required, by excluding any dietary ingredient that is a constituent of a food. According to FDA, ingredients such as proteins, enzymes, or amino acids “present in the food supply” as constituents of food do not qualify under section 350b(a)(1) unless the protein, enzyme, or amino acid has been separately marketed as a food product. This interpretation, as with FDA’s other recent interpretations aimed at limiting the protections of DSHEA, is questionable at best and has no clear basis in the FDCA.