IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF UTAH

CENTRAL DIVISION

NUTRACEUTICAL CORPORATION and SOLARAY, INC., Plaintiffs, vs. LESTER CRAWFORD, D.V.M., Acting Commissioner, U.S. Food and Drug Administration, et al., Defendants.	ORDER Case No. 2:04CV409 TC

Plaintiffs Nutraceutical Corp. and Solaray, Inc., ("Plaintiffs") brought this action against Defendants Lester Crawford, D.V.M., Acting Commissioner of the United States Food and Drug Administration, the United States Food and Drug Administration ("FDA"), Tommy Thompson, Secretary of the Department of Health and Human Services, the Department of Health and Human Services, and the United States (collectively "Defendants"), challenging the validity of the FDA's February 2004 regulation banning all ephedrine-alkaloid dietary supplements. Plaintiffs manufacture and sell an ephedrine-alkaloid dietary supplement.

This matter is before the court on Plaintiffs' motion for summary judgment and Defendants' cross-motion for summary judgment. Plaintiffs, bringing this action under the Declaratory Judgment Act, allege that the FDA's Final Rule violates the Food, Drug and

Cosmetic Act ("FDCA"), as amended by the Dietary Supplement Health and Education Act ("DSHEA"), through an improper determination of adulteration under 21 U.S.C. 342(f)[1], and also that it violates the Administrative Procedures Act ("APA").[2]

Plaintiffs seek to have the court: (1) declare the Final Rule invalid; (2) remand the matter to the FDA for further rulemaking consistent with the court's opinion; and (3) enjoin the Defendants from taking enforcement action against Plaintiffs for their sale of a dietary supplement containing 10 mg or less of ephedrine alkaloids per daily dose.

For the reasons set forth below, the court grants the Plaintiffs' motion for summary judgment and denies the Defendants' cross-motion for summary judgment

I. Background

The ephedrine alkaloids used in dietary supplements are naturally occurring stimulant compounds. Ephedrine-alkaloid dietary supplements ("EDS") have been promoted to achieve weight loss, enhance athletic performance and boost energy.

After extensive review, the FDA concluded that all EDS, regardless of the dose suggested in labeling, present an "unreasonable risk of illness or injury." The FDA regulation ("Final Rule"), published February 11, 2004, bans the distribution of all such products on the basis that they are adulterated within the meaning of the DSHEA.

Plaintiff Solaray (now owned by Plaintiff Nutraceutical), has manufactured and sold an EDS since 1988. Plaintiffs' product contains 375 mg of Ephedra sinica and the labeling

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[1]21 U.S.C. § 342 is the food adulteration provision. Subsection (f) provides the criteria for a determination that a dietary supplement is adulterated. An adulterated food or dietary supplement is not marketable under 21 U.S.C. § 333.

[2]Plaintiffs have voluntarily dismissed their claim of a categorical taking under the Fifth Amendment.

recommends one capsule taken no more than twice each day. The recommended dose yields less than 10 mg of ephedrine alkaloids per day. The Final Rule prohibits Plaintiffs from marketing and selling this product.

A. Regulatory Framework

The DSHEA, enacted in 1994 as an amendment to the FDCA, provides that a dietary supplement is adulterated if it presents "a significant or unreasonable risk of illness or injury under" the conditions of use recommended in labeling. 21 U.S.C. § 342(f)(1)(A).

Under the DSHEA, dietary supplements are regulated as a subset of foods unless the supplement producers make disease claims that bring the supplements within the definition of a drug. See 21 U.S.C. §§ 321(ff)(defining "dietary supplement), (g)(1) (defining "drug"); cf. 21 U.S.C. § 343(r)(6) (identifies claims which many be made by manufacturers of dietary supplements and those which are prohibited). Accordingly, dietary supplement manufacturers are not required to provide evidence of product safety and efficacy before marketing their products. Additionally, the DSHEA does not require dietary supplement manufacturers to comply with the post-market product safety monitoring or reporting requirements that the FDCA requires for drugs. The FDA relies on voluntary studies, voluntarily reported adverse event reports ("AERs"), and other data to identify potential safety problems associated with dietary supplements.

B. FDA's Rulemaking

On February 11, 2004, the FDA published the Final Rule declaring EDS adulterated and not legally marketable in the United States. The Final Rule became effective on April 12, 2004.

The Final Rule was the culmination of a long process beginning in the early 1990s when the FDA began receiving AERs reflecting injury and illness associated with the use of EDS. The administrative record reflecting the rulemaking process contains over 133,000 pages of scientific data, expert reviews, comments submitted by interested persons, and other materials considered.

The FDA considered evidence from three principal sources: (1) the well-known, scientifically established pharmacology of ephedrine alkaloids; (2) peer-reviewed scientific literature on the effects of ephedrine alkaloids; and (3) AERS related to the consumption of EDS. 69 Fed. Reg. 6788 (Feb. 11, 2004). The FDA also commissioned expert reviews of the scientific evidence and assessed the findings of the expert reviews. Id. at 6802, 6805 & 6814.

1. The 1997 Proposed Rule

The FDA initially published a proposed rule regulating EDS in June of 1997. Under the proposed rule an EDS was adulterated if it contained 8 mg or more of ephedrine alkaloids per serving, or if its labeling suggested or recommended conditions of use that would result in an intake of 8 mg or more during a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids. 62 Fed. Reg. 30678, 30691 (June 4, 1997). Additionally, the rule proposed to: (1) prohibit EDS labeling for claims or uses requiring long-term intake to achieve the purported effect; (2) prohibit EDS producers from combining ephedrine alkaloids with other stimulant ingredients; (3) require EDS warning statements that would alert consumers to possible drug interactions, and directing consumers not to take the product for more than seven days; (4) require EDS warning statements providing further advice for at-risk consumers; and (5) require that claims encouraging short-term excessive intake be accompanied with a statement that warned

that the recommended intake may result in serious adverse health effects. Id. at 30691-704.

Upon receiving a request from the House Committee on Science, the Government Accounting Office ("GAO") released a report entitled "Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids." 65 Fed. Reg. 17474 (Apr. 3, 2000). In this report the GAO recommended that the FDA "provide stronger evidence on the relationship between the intake of [EDS] and the occurrence of adverse reactions that support the proposed dosing level and duration of use limits." Id. at 17475. Further, the GAO noted that the FDA "should consider additional information . . . to determine whether a dietary ingredient limit, or some alternative approach, would be appropriate to regulate [EDS]." 65 Fed. Reg. at 17475.

In light of the GAO's conclusions and other comments, on April 3, 2000, the FDA partially withdrew the proposed rule. Specifically, the FDA withdrew the restrictions on dosages and directions for frequency of use and the proposed prohibition on labeling claims for uses encouraging long-term intake. The FDA also withdrew the proposed warnings advising consumers not to exceed the recommended dosages or use the product for more than seven days. The FDA retained the other warning statements and the proposed prohibition on combining EDS with other stimulant ingredients. Id. at 17475-76.

After this partial withdrawal of the proposed rule, the FDA reopened the comment period three times and considered additional evidence.

2. The 2004 Final Rule

The notice reopening the comment period on March 5, 2003, stated that the FDA intended to consider whether the "FDA should determine that [EDS] present a 'significant or unreasonable

risk of illness or injury'" and sought comments on that issue. 68 Fed. Reg. 10417, 10419 (March 5, 2003) (quoting 21 U.S.C. § 342(f)(1)(A)).

The FDA published the Final Rule on February 11, 2004. The FDA concluded that when the minimal benefits of EDS are weighed against the substantial risks, all EDS present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions or use are suggested or recommended in labeling, under ordinary conditions of use. 69 Fed. Reg. at 6788. Because it found that use of EDS does not provide a benefit sufficient to outweigh the increased risk of heart attack, stroke, and death, the FDA concluded that all EDS pose an unreasonable risk and are adulterated under the DSHEA. Id. at 6789.

C. FDA's Statutory Interpretation and the Final Rule

The FDA promulgated the Final Rule under the DSHEA, which provides:

> A food shall be deemed to be adulterated–
> ***
> (f) Dietary supplement or ingredient: safety
> (1) If it is a dietary supplement or contains a dietary ingredient that–
> (A) presents a significant or unreasonable risk of illness or injury under–
> (i) conditions of use recommended or suggested in labeling, or
> (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;
> . . .
> 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.

21 U.S.C. §342(f)(1).

The summary of the Final Rule closely follows the language of the statute:

> The [FDA] is issuing a final regulation declaring dietary supplements containing ephedrine alkaloids adulterated under the [FDCA] 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.

69 Fed. Reg. at 6788.

The FDA concluded that the words "significant" and "unreasonable" have two separate and independent meanings. Under the FDA's statutory construction, "significant" involves an evaluation of risk alone, while "unreasonable" requires a comparison of risks and benefits. Id. at 6823 ("A risk could be significant, but reasonable if the benefits were great enough to outweigh the risks."). The Final Rule does not include a consideration of the word "significant." The record indicates that the FDA believed that evaluation of EDS under the "significant" standard was unnecessary because it is included within the statute as an alternative to "unreasonable." Id. at 6788 & 6822-23 (see also Def. Mem. Supp. Cross-Mot. Summ. J. at 31 n.14 ("Because the FDA concluded that EDS pose an unreasonable risk, it was not necessary for the agency to address DSHEA's significant risk standard.").

D. The FDA's Findings

EDS have been promoted to help achieve weight loss, enhance athletic performance, increase energy levels, ease breathing, and for other similar uses. The FDA determined that these effects are temporary, of modest benefit, and do not improve health if they occur at all. 69 Fed. Reg. at 6822 & 6826. The FDA found that although there is evidence to support modest, short-term weight loss, the FDA could not determine whether that weight loss results in improved

health outcomes. Specifically, the FDA could not determine whether EDS have a positive effect on cardiovascular risk factors associated with being overweight. Id. at 6789, 6818-21, 6825-26.

The FDA found that EDS, generally, increase the risk of serious adverse events, including heart attacks, stroke, and death. Id. at 6789, 6800-04. An evaluation of single-dose studies showed that EDS cause an increase in heart rate and blood pressure in healthy subjects. A multiple-dose study demonstrated a higher blood-pressure measurement after one month of continued exposure to a combination of EDS and caffeine. Id. at 6801-02. The FDA also reviewed studies observing increased mortality in people with congestive heart failure who were treated with substances similar to EDS. Id. Additional evidence of the negative effects of EDS was obtained through 3,000 AERs submitted directly to the FDA and 16,000 reports from records maintained by Metabolife, one of the largest distributors of EDS.

Plaintiffs' product is labeled with a recommended daily dose of approximately 10 mg of ephedrine alkaloids. Therefore, the key evidence is that which the FDA contends shows a significant or unreasonable risk of illness or injury at recommended dosages of 10mg per day or less. The FDA points the court to 69 Fed. Reg. 6788, References 84-87 ("Reference") as the relevant sections.

References 84 and 85 are a series of letters between the FDA and Dr. Mario A. Inchiosa written between May and July of 1999. The letters are a response by Dr. Inchiosa to a request from the FDA that he conduct a scientific review on the effects of ephedrine alkaloids. The letters contain Dr. Inchiosa's conclusions derived from the examination of various studies of intake of

substances similar to ephedrine. Dr. Inchiosa performed a pharmacokinetic analysis[3] comparing epinephrine to ephedrine. According to Dr. Inchiosa, epinephrine and ephedrine alkaloids produce similar effects in the human body, but at different potencies.[4] He also used studies of the effects of injections of epinephrine to derive conclusions about the effects of ephedrine alkaloids. Acceptance of Dr. Inchiosa's conclusions depends on the acceptance of a mathematical model used to compare doses of epinephrine to ephedrine.

Dr. Inchiosa specifically refers to a study performed by W.E. Clutter, et al., ("Clutter Study"), in which the administration of epinephrine increased heart rate and blood pressure. See W.E. Clutter, et al., Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolis and hemodynamic actions in man, 1980 J. Clin. Invest. 66, 94-101 (cited in Reference 84 at 4 & 6). Dr. Inchiosa's mathematical model demonstrates that a "chronic ephedrine dose of 1.5 mg every four hours"would produce the same effects as epinephrine did in the Clutter Study. Reference 84 at 4. Dr. Inchiosa concluded that: "In the absence of a clinical indication, it would not be possible to recommend a safe dose of ephedra." Id. Other than the conclusions about ephedrine drawn from the Clutter Study on the effects of epinephrine, there is no evidence in the administrative record pertaining specifically to doses of ephedrine at the ephedrine- alkaloid levels recommended by Plaintiffs, that is, 10 mg per day.

References 86 and 87 are excerpts from the transcript of the FDA's Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids Meeting held on August 26-

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[3]A pharmacokinetic analysis is one which examines the bodily absorption, distribution, metabolism, and excretion of drugs. Webster's New Collegiate Dictionary 852 (G. & C. Merriam 1979).

[4]In Reference 84, Dr. Inchiosa indicates that various studies have shown that epinephrine is between 41 and 69 times more potent than ephedrine. These potency ratios serve as the basis of his analysis. Reference 84 at 4-5.

27, 1996. The transcript demonstrates that several physicians and researchers were unable to conclude that there is a safe dosage level for EDS. For example, Dr. Georgitis stated, "I obviously cannot identify [a safe level]. There's no scientific data which shows that 1 milligram is any better than 5, which is any better than 10, which is any better than 30, and that goes both for the ephedrine alkaloid and for ephedrine itself." Reference 86 at 136. Dr. Ricaurte noted that part of the difficulty in identifying a safe level of EDS is that "[t]here is uncertainty . . . [in] the available data with regard to the ephedrine alkaloids themselves[.]" Id. at 221. Dr. Marangell expressed concern regarding "the serious adverse events in the 1- to 5- milligram range. . . . [W]e don't have a lot of data on that, and perhaps for many people that's fine, but . . . individual variation is going to play as much of a role as a particular dose level is." Id. at 229. Reference 87 duplicates much of what is discussed in Reference 86.

In sum, those present at the meeting concluded that it is difficult or impossible to identify any safe recommended dosage level for EDS.

II. Analysis

The parties' motions ask the court to determine whether the Final Rule banning all EDS violates 21 U.S.C. 342(f). To resolve this issue the court must answer: first, whether the FDA's use of a risk-benefit analysis is appropriate under the DSHEA; and second, whether the FDA has provided sufficient evidence to support the conclusion that EDS containing 10 mg or less per day of ephedrine alkaloids pose a significant or unreasonable risk of illness of injury.[5]

[5]Because of the court's answers to these two questions, it need not determine whether the FDA properly omitted the term "significant" from its construction of the statute or whether it complied with the notice and comment procedures of the APA.

A Scope of Review

While styled as cross-motions for summary judgment, this is actually an appeal from the decision of an administrative agency. Accordingly, the court must apply the standards for an appeal. See Olenhouse v. Commodity Credit Corp., 42 F.3d 1560, 1580 (10th Cir. 1994); Southern Utah Wilderness Alliance v. B.L.M., 147 F.Supp. 2d 1130, 1135-36 (D.Utah 2001). In a review of an administrative decision under the APA, the parties are typically not permitted to supplement the evidence in the administrative record. See e.g., Roberts v. Morton, 549 F.2d 158, 160 (10th Cir. 1976) ("Such review is confined to the agency record or such portions of it which the parties may cite, and additional evidence is not to be admitted.") (citing Nickol v. United States, 501 F.2d 1389, 1390 (10th Cir. 1974)).

B. Deference

The final sentence of 21 U.S.C. §342(f) provides that: "The court shall decide any issue under this paragraph on a de novo basis." The parties agree that this provision requires the court to examine all factual determinations on a de novo basis. The parties do not agree, however, on whether the court should review the FDA's statutory construction de novo or whether the court should accord the FDA's conclusions deference under Chevron USA, Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837 (1984). The court, reviewing the Final Rule under Chevron, need not reach the question of whether the FDA's statutory construction should be reviewed de novo.

Under Chevron, a court must first determine whether Congress has spoken to the precise question at issue. Chevron, 467 U.S. at 842; see also FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000); Pharmanex v. Shalala, 221 F.3d 1151, 1154 (10th Cir. 2000). If

Congress' intent is clear and unambiguous, the analysis is complete and Congress' intent controls. "In a statutory construction case, the beginning point must be the language of the statute, and where the statute speaks with clarity to an issue[,] judicial inquiry into the statute's meaning . . . is finished." Estate of Cowart v. Nickols Drilling Co., 505 U.S. 469, 475 (1992).

"As a general rule of statutory construction, a statute is ambiguous if it is 'capable of being understood in two or more possible senses or ways.'" Houghton ex. rel. Houghton v. Reinertson, 382 F.3d 1162, 1169 (10th Cir. 2004) (quoting Chickasaw Nation v. United States, 534 U.S. 84, 90 (2001)); see also, Allen v. Geneva Steel Co., 281 F.3d 1173, 1178 (10th Cir. 2002) ("[A]mbiguity exists when a statute is capable of being understood by reasonably well-informed persons in two or more different senses.") (quotation omitted). The ambiguity of a statute is determined "by reference to the language itself, the specific context in which the language is used, and the broader context of the statute as a whole." Houghton, 382 F.3d at 1169 (citing Robinson v. Shell Oil Co., 519 U.S. 337, 341 (1997)).

If a court finds that the statute is silent or ambiguous as to the specific issue, the question is whether the agency's answer is "based on a permissible construction of the statute." Chevron, 467 U.S. at 842-43. Under Chevron, a court must accord deference to an administrative agency's reasonable interpretation of a statute. Chevron, 467 U.S. at 843-44 & n.11; see also United States v. Mead Corp., 533 U.S. 218, 229 (2001) ("reviewing court has no business rejecting an agency's exercise of its generally conferred authority to resolve a particular statutory ambiguity simply because the agency's resolution seems unwise") (citations omitted). A court must "give effect to the agency's interpretation unless it is arbitrary, capricious, or manifestly contrary to the statute." Pharmanex, 221 F.3d at 1154. The decision as to what a statute means, however, is "the

quintessential judicial function." BATF v. FLRA, 464 U.S. 89, 98 (1983). The question of statutory interpretation ultimately rests with the court. Chevron, 467 U.S. at 843 n. 9.

With these principles in mind, the court turns to the questions at issue.

C. Was the FDA's use of a risk-benefit analysis appropriate under the DSHEA?

In promulgating the Final Rule, the FDA relied upon a risk-benefit test to determine whether the risk presented by EDS is unreasonable and argues that this is a proper construction of the statute. 69 Fed. Reg. at 6788. Plaintiffs have asserted that the application of this test is an improper interpretation of the statute because it adds language not intended by Congress and has the effect of shifting the burden of proof from the government to the manufacturers of EDS contrary to Congress' intent to harmonize the treatment of dietary supplements with that of food generally. The plain language of the DSHEA does not require a comparison of benefits and risks.

The pertinent portion of 21 U.S.C. 342(f) states that a dietary supplement shall be deemed adulterated if it "presents a significant or unreasonable risk of illness or injury." 21 U.S.C. 342(f)(1)(A). The FDA contends that the plain meaning of the term "unreasonable" in the statute requires a risk-benefit analysis: "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." 69 Fed. Reg. at 6788. The FDA argues that this construction is consistent with Congress' definition of the term "unreasonable risk" in other parts of the same statute and other portions of similar statutes. Specifically, the FDA refers the court to the provisions of the FDCA governing medical devices and also the Toxic Substances Control Act ("TSCA"). See 21 U.S.C. §360c(a)(1); H. Rep. 94-853, 94th Cong. 2d Sess. 19 (1976) ("the requirement that risk be unreasonable

contemplates a balancing of the possibility that illness or injury will occur against the benefits of use."); 15 U.S.C. §2605(a); H. Rep. 94-1341, 94th Cong., 2d Sess. 14 (1976) (defining "unreasonable risk" in the context of the TSCA as "balancing the probabilities that harm will occur and the magnitude and severity of that harm against the effect of proposed regulatory action on the availability to society of the benefits of the substance or mixture").

Defendants' reliance on the medical device provisions of the FDCA to justify the inclusion of a risk-benefit test for dietary supplements is misplaced. The provision governing the safety and effectiveness of medical devices specifically calls for a risk-benefit analysis:

> For purposes of this section and sections 360d and 360e of this title, the safety and effectiveness of a device are to be determined--
>
> . . .
>
> (C) weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.

21 U.S.C. § 360c(a)(2) (emphasis added). The DSHEA contains no such provision. Unlike medical devices and drugs, dietary supplements are not classified on the basis of a risk-benefit analysis. Cf. 21 U.S.C. §§ 355(b) (requiring that an application for a new drug show that it is effective for its intended use); 360c(a)(1)(A),(B) & (C) (all three classes of medical devices have effectiveness requirements).

The FDCA, in defining dietary supplements, states: "Except for the purposes of section 201(g), a dietary supplement shall be deemed a food within the meaning of this Act." 21 U.S.C. § 321(ff). A brief look at the legislative history of the DSHEA indicates that Congress generally intended to harmonize the treatment of dietary supplements with that of foods when it added the dietary supplement subsection to the food adulteration provision. Sen. Rep. No. 103-410 at 21

("Section 402 [of the FDCA] is the provision that establishes the grounds upon which the [FDA] may deem a food (including a dietary ingredient) to be adulterated"). "Under present law, a dietary supplement, as with any food, is presumed to be safe." Id. at 22 (emphasis added). Food producers are not required to establish a benefit before sale.[6]

The FDA's imposition of a risk-benefit analysis places a burden on the producers of EDS to demonstrate a benefit as a precondition to sale, and that is contrary to Congress' intent. Congress unequivocally stated that "[i]n 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." 21 U.S.C. 342(f). Proof of adulteration is the sole responsibility of the FDA: "[A dietary supplement, as with any food,] may be lawfully marketed, unless and until the FDA, by a preponderance of the evidence, shows that the supplement is 'injurious to health.'" Sen. Rep. No. 103-410 at 21. The imposition of a risk-benefit analysis requires the producer of an EDS to establish a benefit and alleviates the burden Congress placed squarely on the government to demonstrate the existence of a significant or unreasonable risk.

For the above reasons, the court concludes that the FDA's requirement that EDS demonstrate a benefit is contrary to the clear intent of Congress. For those same reasons, the FDA's definition of "unreasonable" entailing a risk-benefit analysis is also improper.

D. Has the FDA provided evidence to support the conclusion that EDS containing 10 mg or less per day of ephedrine alkaloids pose a significant or unreasonable risk of illness of injury?

Under 21 U.S.C. §342(f), "the United States shall bear the burden of proof on each

[6]As pointed out by Plaintiffs, if food producers were required to show a benefit as a precondition to sale, the sale of foods such as potato chips might be prohibited.

element to show that a dietary supplement is adulterated." The government must establish that EDS pose a significant or unreasonable risk by a preponderance of the evidence. See Sen. Rep. No. 103-410 at 36 ("By the last sentence of [§342(f)], it is intended to codify current law that the government bear the burden of proving dietary supplements adulterated. The government must produce the preponderance of the evidence as to the harmful effects from the dietary supplement when used as recommended and suggested in the labeling." (citing United States v. 71/55 Gallon Drums of Stuffed Green Olives, 790 F. Supp. 1379 (N.D. Ill. 1992)).[7]

The statute reads that the government's burden is met only if it has demonstrated the presence of a risk "under conditions of use recommended or suggested in labeling." 21 U.S.C. §342(f)(1)(A)(i). The plain language of the statute requires a dose-specific analysis. Legislative history also confirms Congress' intent to require that a finding of adulteration be dose-specific: "a safety finding cannot be entered against a supplement based upon a dosage not recommended to consumers in the labeling." Sen. Rep. No. 103-410 at 36.

Simply stated, to declare all EDS adulterated, as it has done, the FDA must prove that any dose amount, no matter how small, presents a significant or unreasonable risk of illness or injury. Specifically, because the Plaintiffs' suggested dosage recommends no more than 10 mg of ephedrine alkaloids per day, the proper focus here is on the evidence the FDA presented regarding the risks of low-dose EDS. To this end, the Defendants have directed the court specifically to 69

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[7] The courts have long required the FDA to prove adulteration by a preponderance of the evidence. See United States v. 5 Cases More of Less Containing 'Figlia Mia Brand', 179 F.2d 519, 524 (2d Cir. 1950) ("This is a civil proceeding in which the usual rule as to burden of proof [preponderance of the evidence] prevails."); 71/55 Gallon Drums of Stuffed Green Olives, 790 F. Supp. at 1382 ("The burden of proof rests on the government to establish by a 'fair preponderance of the evidence' that the article of food is adulterated within the meaning of §342(a)(3)." (citation omitted)); see also United States v. Tins of Strawberries, 175 F. Supp. 694, 699 (D.Ark. 1959); United States v. Anderson Seafoods, Inc., 447 F. Supp. 1151 (N.D.Fla. 1978) ("A preponderance of the evidence shows that some unquantified portion of the mercury in swordfish is attributable to the acts of man.").

Fed. Reg. 6788, References 84, 85, 86, and 87.

Reference 84, the Inchiosa review, concludes that "a chronic ephedrine dose of 1.5 mg every 4 hours" (a daily dose of 9 mg) would cause "increases in heart rate and systolic blood pressure." Reference 84 at 4. This conclusion, contained in one six-page letter to the FDA, is the only specific reference in the administrative record to the effects of low-dose EDS. The Inchiosa review derives the potential physiological effects of orally ingested ephedrine from data obtained regarding intravenous injections of epinephrine. He used a hypothetical mathematical model to perform a pharmacokinetic analysis of the effects of ephedrine alkaloids. There is no specific data involving the oral ingestion of 10 mg per day of EDS.[8]

Dr. Inchiosa's conclusions rest on a comparison of potency rates between epinephrine and ephedrine alkaloids. Dr. Inchiosa reviewed studies indicating that epinephrine is between 41 and 69 times more potent than ephedrine. Id. at 1-2. The data and its application to ephedrine alkaloids are applicable only upon acceptance of Dr. Inchiosa's mathematical model. In Reference 85, however, Dr. Inchiosa also states that the onset of the effects of ephedrine alkaloids would vary depending on the source of the alkaloids and the actual rates of absorption which weakens his general conclusions regarding the intake of low-dose EDS. Reference 85 at 1-2. Dr. Inchiosa's conclusion that 9 mg per day of ephedrine alkaloids produces negative health effects is based upon chronic intake, which is not the condition of use suggested on the labeling of Plaintiffs' product. This evidence cannot, on its own, support a conclusion that a recommended

[8]The only dose-specific data provided by Dr. Inchiosa pertaining to low-dose EDS is that the harmful effects of ephedrine would be felt with a "chronic ephedrine dose of 1.5 mg every four hours." Reference 84 at 4. This data was derived not from a study involving the oral ingestion of ephedrine alkaloids, but from a derivative analysis relying on Dr. Inchiosa's mathematical model.

dose of 10 mg per day of EDS presents a significant or unreasonable risk.

Dr. Inchiosa also states that he cannot determine a safe level of EDS intake. This sentiment is echoed throughout the transcript of the FDA's Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids Meeting held on August 26-27, 1996 (References 86 and 87). Several of the meeting's attendees made comments that a safe level could not be determined. There was, apparently, not enough evidence to support the conclusion that there is a safe level of intake for EDS.

A negative inference is different from the affirmative proof required by 21 U.S.C. 342(f). The statute requires an affirmative demonstration of "significant or unreasonable" risk at a particular dose level to support a finding of adulteration. There is not sufficient evidence in the administrative record to establish that the risks identified by the FDA are associated with the intake of low-dose EDS. The statement that a safe level cannot be determined is simply not sufficient to meet the government's burden. To find otherwise would be to place the burden on the manufacturers of EDS to show that their recommended dosages are safe. This would be directly contrary to the statutory language placing the burden of proof on the government and to the intent of Congress in regulating dietary supplements as food.

The FDA, by failing to prove by a preponderance of the evidence that a dosage of 10 mg or less of ephedrine alkaloids presents a significant or unreasonable risk of illness or injury, has failed to give effect to the dose-specific language of 21 U.S.C. §342(f)(1)(A)(i).

ORDER

Accordingly, Plaintiffs' motion for summary judgment (Dkt. 7) is GRANTED and Defendants' cross-motion for summary judgment (Dkt. 14) is DENIED.

The court remands to the FDA for further rulemaking consistent with this Order and enjoins Defendants from taking enforcement action against Plaintiffs for their sale of a dietary supplement containing 10 mg or less of ephedrine alkaloids per daily dose.

SO ORDERED this 13 day of April, 2005.

BY THE COURT:

Tena Campbell

TENA CAMPBELL
United States District Judge