

labeling, promotional material, advertising, and 'any other relevant source'" (557 F.2d at 334 (citations omitted)). See also § 201.128 (listing evidence FDA will consider in determining the intended use of a drug).

(104.) One comment said that the proposal must be withdrawn because, contrary to section 403(r)(6) of the act, it gives manufacturers the burden to prove that a claim is not a drug claim when, in fact, FDA has the burden, by a preponderance of relevant evidence, to establish that a dietary supplement is misbranded. The comment cited two court opinions, United States v. 29 Cartons * * an Article of Food (Oakmont), 987 F.2d 33 (1st Cir. 1993) and United States v. An Article of Food * * * Viponte Ltd. Black Currant Oil, 984 F.2d 814 (7th Cir. 1993), for the proposition that, before DSHEA was enacted, courts had invalidated an FDA enforcement theory that shifted the burden of proof to manufacturers.

FDA disagrees with this comment. Although the comment is correct that FDA has the burden of proving that a dietary supplement--or, in fact, any food--is misbranded, the rule does not give manufacturers the burden of proving that a claim is not a drug claim. The rule does not shift the burden of proof in an enforcement action but rather sets forth criteria for what claims are disease claims that may subject a product marketed as a dietary supplement to regulation as a drug.

The two cases cited in the comment are inapposite. They concern FDA's efforts to regulate certain dietary ingredients as food additives and do not have any relevance to claims issues.

(105.) One comment said that the proposed rule is inconsistent with the act and congressional intent, arguing that, by enacting DSHEA, Congress had taken steps to reverse FDA's "overly restrictive" approach towards claims and had commanded the agency to expand, rather than restrict, the amount of health information permitted on dietary supplement labels and labeling. According to the comment, the proposal "directly and substantially violates the overall statutory scheme and the expressed legislative intent" and FDA "has no authority to proceed with the rulemaking without a grant of authority from Congress in light of the Act's language and Congressional intent."

The agency disagrees with this comment and believes that the rule is consistent with the act and congressional intent. Although Congress, in enacting DSHEA, did expand the scope of information in dietary supplement labeling by providing for claims to affect the structure or function of the body and the other types of claims authorized by section 403(r)(6) of the act, Congress also explicitly limited statements under section 403(r)(6) to those that do not claim to "diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases."

This rule does not create new restrictions but merely implements the provisions of section 403(r)(6) of the act. FDA has authority to issue implementing regulations under section 701(a) of the act, which authorizes the agency to issue regulations for the efficient enforcement of the act.

(106.) One comment declared that FDA has no legal basis to include a broad variety of implied claims.

FDA disagrees with this comment. The agency has regulated implied claims in labeling for many years, in many contexts. (See, e.g., 21 CFR 104.5(b) and (d) (prohibiting certain implied claims relating to compliance with nutritional quality guidelines); 21 CFR 101.13(a) (classifying implied claims to characterize the level of a nutrient in food as nutrient content claims subject to the same requirements as express claims); 21 CFR 101.95 (prescribing conditions under which implied claims of freshness may be made for foods); 21 CFR 201.10(c)(3) (prohibiting use in ingredient statement of fanciful drug or ingredient names that falsely imply that the drug or ingredient has some unique effectiveness or composition); 21 CFR 201.302(c) (prohibiting implied claims that drugs for internal use that contain mineral oil are for administration to infants). The agency has also regulated implied claims in prescription drug advertising. (See, e.g., § 202.1(a)(3) (21 CFR 202.1(a)(3)) (prohibiting use in advertising of fanciful product or ingredient

names that falsely imply that the drug or ingredient has some unique effectiveness or composition); § 202.1(e)(6)(v)

(prohibiting implied claims that a study represents more widespread experience with the drug than it actually does).)

More specifically, the agency has repeatedly taken the position that implied disease claims in labeling subject a product to regulation as a drug. In the animal drug context, § 500.52 (21 CFR 500.52) provides that the use of certain terms in the labeling of products intended for use in or on animals implies that the product is capable of a therapeutic effect and causes the product to be a drug within the meaning of section 201(g) of the act. In the human drug context, § 201.56(c) (21 CFR 201.56(c)) prohibits "implied claims or suggestions of drug use" in prescription drug labeling unless the product has been shown to be safe and effective for the implied or suggested use. (See also § 310.530 (21 CFR 310.530) (use of the word "hormone" in labeling is an implied drug claim).) Moreover, courts have upheld FDA's authority to regulate implied drug claims. (See, e.g., United States v. Storage Spaces Designated Nos. "8" and "49", 777 F.2d 1363, 1366 & n. 5 (9th Cir. 1985), cert. denied, 479 U.S. 1086 (1987); Pasadena Research Labs., Inc. v. United States, 169 F.2d 375, 383 (9th Cir.), cert. denied, 335 U.S. 853 (1948); United States v. Six Dozen Bottles * * * "Dr. Peter's Kuriko", 158 F.2d 667, 669 (7th Cir. 1947); United States v. John

J. Fulton Co., 33 F.2d 506, 507 (9th Cir. 1929); Bradley v. United States, 264 F. 79, 81-82 (5th Cir. 1920); United States v. Kasz Enterprises, Inc., 855 F. Supp. 534, 539, 543-44 (D.R.I. 1994), modified on other grounds, 862 F. Supp. 717 (D.R.I.1994); United States v. 43 ½ Gross Rubber Prophylactics, 65 F. Supp. 534, 535 (D. Minn. 1946), aff'd sub nom. Gellman v. United States, 159 F.2d 881 (8th Cir. 1947)..)

(107.) Many comments argued that the proposed rule ignored the Supreme Court decision in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993).

FDA disagrees with these comments. The comments did not explain how the rule was contrary to or even affected by the decision. Daubert involved the admissibility of scientific evidence in a judicial proceeding under the Federal Rules of Evidence. This rulemaking does not present issues regarding the admissibility of evidence in any proceeding, judicial or administrative, nor does it address expert testimony (which was at issue in Daubert). Thus, FDA does not agree that the rule "ignores" or is contrary to the Daubert decision.

C. Constitutional Issues

1. First Amendment

(108.) Several comments focused on the First Amendment. One comment argued that the rule violates the First Amendment because it is more restrictive than is necessary to advance FDA's

interests. The comment conceded that the government may regulate or prohibit commercial speech if the speech is inherently false, deceptive, or misleading, but argued that the government can only restrict commercial speech that is not false, deceptive, or misleading if the government shows that the restriction directly and materially advances a substantial state interest in a manner that is no more extensive than necessary to serve that interest (citing Ibanez v. Florida Dept. Of Bus. & Prof'l Regulation, 512 U.S. 136, 142 (1994); Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 566 (1980)). The comment argued that not all structure/function claims prohibited under the proposed rule are inherently false or misleading and that if FDA does not review the evidence for a claim, the claim does not become false or misleading. Although the comment admitted that FDA has a substantial interest in regulating the safety, efficacy, and labeling of dietary supplements in order to protect the public health, the comment claimed that the regulation was more extensive than necessary. The comment argued that a disclaimer is "the constitutionally mandated method of regulating commercial speech."

Other comments said the proposed rule violates the First Amendment because, using the analysis in Central Hudson Gas & Electric Corp. v. Public Service Commission, 447 U.S. 557 (1980), it is not narrowly tailored to meet FDA's interests and does not

directly and materially advance the agency's interests. In general, these comments offered various reasons why the proposed rule did not survive scrutiny under Central Hudson. For example, under Central Hudson, the government may regulate commercial speech that concerns unlawful activity or is misleading if, among other things, the government asserts a substantial interest in support of its regulation. In brief, the comments said FDA failed to assert a substantial interest or construed the government's interest to be Congress' interest in increasing the amount of information to consumers. Others said that, contrary to Central Hudson, the proposed rule was not narrowly tailored and suppressed more speech than necessary to protect a possible government interest in protecting consumers from fraud and protecting public health and either suggested alternatives or said FDA should consider less restrictive alternatives. Some comments said the proposal also did not advance the asserted government interest because it blurred, instead of clarified, the line between drug and dietary supplement claims.

One comment also asserted that there is no substantial government interest involved, because FDA has not shown a concern for consumer safety or a danger to public health; according to this comment, the proposed rule was a response to confusion by manufacturers and consumers about what claims are permitted.

Some comments also argued that FDA has not shown that the claims are misleading or that the commercial speech covered by the proposed rule is inherently misleading. One comment asserted that, if statements were untruthful or misleading, DSHEA would have prohibited them.

Another comment said the proposal "trenches on" the First Amendment because consumers have the right to receive, and manufacturers have the right to express, non-misleading information. The comment cited Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998) for this proposition. Another comment cited the Washington Legal Foundation decision to argue that the proposed rule would "impermissibly curtail" the flow of information to consumers. The comment suggested that less restrictive alternatives, such as "allowing implicit, but not explicit, claims," establishing "categories of diseases that clearly denoted drug claims" or identifying terms that connote "treatment," "cure," or "mitigation" exist.

A few comments simply claimed that the proposal violates the First Amendment because it would decrease the amount of scientific information on labels and labeling or because it represents a "prior restraint" on health claims. Other comments objected to particular provisions of the proposed rule on First Amendment grounds, notably proposed § 101.93(g)(2)(iv)(C), which provided that citation of the title of a scientific reference in

dietary supplement labeling would be a disease claim if the title referred to a disease use of the product. Several comments said that this provision of the proposed rule would violate the First Amendment as an unlawful restraint on commercial speech. Others characterized the proposed provision as simply a restriction on freedom of speech, whether the restriction was on the right of companies to provide the information or on the right of consumers to receive the information. One comment said that references to publication titles could be prohibited if they were misleading, but that the rule should not contain a blanket prohibition. Some comments added that the agency should reconsider its position on this provision in light of Washington Legal Foundation v. Friedman.

Finally, a comment said that the proposal was contrary to the decision of the U.S. Court of Appeals for the District of Columbia Circuit in Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999). According to the comment, the court of appeals' First Amendment ruling in *Pearson* requires the agency to permit health claims that do not satisfy the "significant scientific agreement" standard as long as the claim can be rendered non-misleading by requiring a disclaimer. According to the comment, the court's decision also requires FDA to further define the "significant scientific agreement" standard for authorizing dietary supplement health claims. The comment said that the proposed rule was

premature in light of the need to amend the health claims regulations to conform to the Pearson decision. The comment also argued that, in light of Pearson, FDA may not issue a final rule that prohibits disease claims but rather must choose the less restrictive alternative of permitting such claims provided that they are accompanied with disclaimers.

FDA does not believe that the rule violates the First Amendment. The rule does not prohibit any speech; rather, it clarifies the circumstances under which FDA will consider a certain type of speech--labeling claims--to be evidence of intended use as a drug, absent health claim authorization. Thus, the rule does not regulate speech as such, but rather as evidence of intended use. The use of speech as evidence of a company's intended use for its products is constitutional because "[t]he First Amendment * * * does not prohibit the evidentiary use of speech * * * to prove motive or intent" (Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993).) (See also Village of Hoffman Estates v. Flipside, 455 U.S. 489, 495-96 (1982) (upholding village ordinance treating the proximity of drug-oriented literature as evidence that items were marketed for use with illegal drugs). Because it is the intent and not the speech that triggers a regulatory burden on the speaker, there is no First Amendment violation. (See Wisconsin v. Mitchell, 508 U.S. at 489; United States v. Articles of Drug * * * B-Complex Cholinol Capsules, 362

F.2d 923, 927 (3d Cir. 1966) (no impingement on free speech for FDA to use statements made by a lecturer employed by a manufacturer as evidence of the manufacturer's intent that its products be used for therapeutic purposes).)

Even if the rule were viewed as a direct restriction on speech, it would not violate the First Amendment. The marketing in interstate commerce of a drug that has not been determined by FDA to be safe and effective is illegal (see section 301(a) and (d) of the act (21 U.S.C. 331(a) and (d)) and 505 of the act. Thus, labeling claims that promote a dietary supplement for disease uses promote the product for use as an unapproved new drug, which is illegal. Speech promoting an illegal activity may be restricted without violating the First Amendment (Central Hudson, 447 U.S. at 563-564). In Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations, 413 U.S. 376 (1973), the Supreme Court held that an advertisement could be prohibited where it indicated that the advertiser was likely to have an illegal intent while engaging in the proposed transaction (id. at 389). There, as here, "the restriction * * * is incidental to a valid limitation on economic activity" (id.).

Nor does the rule create an unconstitutional prior restraint. FDA does not believe that the regulations in § 101.93(f) and (g) are properly analyzed as a prior restraint at all. As explained previously, the regulations do not restrict

speech but rather treat it as evidence of a product's intended use. Using speech to infer intent does not violate the First Amendment (Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993)). Thus, the regulations do not prevent speech from happening, but, as evidence of intended use, they determine the consequences that result from certain types of speech. (See Village of Hoffman Estates v. Flipside, 455 U.S. at 495-96 (rejecting head shop's "exorbitant" claim that village ordinance treating the proximity of drug-oriented literature as evidence of intended use was a prior restraint).)

Although the regulations cannot themselves be considered as a direct prior restraint, it is true that claims classified as disease claims under the regulations are subject to prior authorization requirements that could be considered prior restraints--namely, the prior authorization requirement for dietary supplement health claims and the new drug approval requirements that are triggered in the absence of health claim authorization. In both cases, a disease claim cannot be made until FDA has evaluated the safety of the product and the evidence supporting the claim. However, labeling claims are commercial speech, and the Supreme Court has indicated that the prior restraint doctrine may not apply to commercial speech. (See Central Hudson, 447 U.S. at 571 n.13 ("[C]ommercial speech is such a sturdy brand of expression that traditional prior

restraint doctrine may not apply to it."; Virginia State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 771-72 n.24 (1976) (greater objectivity and hardiness of commercial speech may make prior restraint doctrine inapplicable). Commercial speech is "sturdy" because of its profit motive. "[S]ince advertising is the sine qua non of commercial profits, there is little likelihood of its being chilled by proper regulation and forgone entirely" (Virginia State Bd. of Pharmacy, 425 U.S. at 771-72 n.24). The same is true of labeling. The Supreme Court has expressed approval of prior review requirements in commercial speech cases. (See Shapero v. Kentucky Bar Ass'n, 486 U.S. 466, 476 (1988) (lawyer may be required to file solicitation letter with State in advance, to give it "ample opportunity to supervise mailings and penalize actual abuses"); Central Hudson, 447 U.S. at 571 n.13 (State may require "a system of previewing advertising campaigns").)

If the prior authorization requirement for dietary supplement health claims and the approval requirement for new drugs were to be considered prior restraints, they would be constitutional prior restraints. The only court of appeals to address the issue in the health claims context ruled that the health claims authorization process is not an unconstitutional prior restraint. In a recent case challenging the NLEA and FDA's health claim regulations for dietary supplements, the U.S. Court

of Appeals for the Second Circuit held that the prior restraint doctrine did apply, but it went on to uphold the statute and regulations based on consideration of the Central Hudson factors. Nutritional Health Alliance v. Shalala, 144 F.3d 220, 227-28 (2d Cir.), cert. denied, 119 S. Ct. 589 (1998). In Nutritional Health Alliance, the Second Circuit held that the health claims authorization process is "sufficiently narrowly tailored" and has adequate procedural safeguards--including a deadline for final agency action, a decision making standard to constrain the agency's discretion, and provision for development of a record for judicial review--to render it constitutionally valid (144 F.3d at 228; see § 101.70 (procedures for petitioning for a health claim)). In upholding the regulatory scheme, the court also stressed that matters of public health and safety were involved (144 F.3d at 228). The same considerations that the court in Nutritional Health Alliance relied on also operate in the new drug approval context: Matters of public health and safety are involved, and the act and implementing regulations provide many procedural safeguards, including a deadline, a decision making standard, and the development of an record for judicial review (see section 505(c)(1), (d), and (h) of the act and; 21 CFR 314.200.) Moreover, as far as FDA is aware, the constitutionality of the new drug approval process has never been challenged on First Amendment grounds. Therefore, FDA does not

believe that the prior restraint argument in the comments has merit.

Many of the comments assumed that the test for restrictions on commercial speech set forth by the Supreme Court in Central Hudson applies. FDA believes that it is not necessary to reach the Central Hudson test because the rule is constitutional under Wisconsin v. Mitchell, Pittsburgh Press, and Village of Hoffman Estates; however, the rule also easily passes muster under the four-part test in Central Hudson. Under that test, the first question is whether the commercial speech at issue is false, misleading, or concerns unlawful activity, because such speech is beyond the First Amendment's protection and may be prohibited. If the speech is truthful, non-misleading, and concerns lawful activity, the government may nonetheless regulate it if the government interest asserted to justify the regulation is substantial; the regulation directly advances the asserted governmental interest; and the regulation is no more extensive than necessary to serve the government interest (Central Hudson, 447 U.S. at 566). The Supreme Court has explained that the last element of the test is not a "least restrictive means" requirement, but rather requires narrow tailoring--"a fit that is not necessarily perfect, but reasonable" between means and ends (Board of Trustees of the State Univ. of N.Y. v. Fox, 109 S. Ct. 3028, 3032-35 (1989)). In subsequent decisions, the Court has

also clarified that "misleading" in the first element of the test refers to speech that is inherently or actually misleading.

Thus, if the speech to be regulated is not inherently or actually misleading, the remainder of the test applies. (See In re R.M.J., 455 U.S. 191, 203 (1982).)

As previously discussed, FDA believes that claims for disease uses that have not been found to be safe and effective are speech related to an unlawful activity, and therefore there is no need to reach the remaining elements of the Central Hudson test. The agency also considers such claims inherently misleading because, when accompanied by a disclaimer that directly contradicts the claim by stating that the product is not intended to have an effect on disease, they are inherently likely to confuse consumers rather than provide them with useable information. Speech that is "more likely to deceive the public than to inform it" is not protected by the First Amendment (Central Hudson, 447 U.S. at 563). If not inherently misleading, claims for disease uses that have not been found to be safe and effective are at least potentially misleading because of the confusion caused by the disclaimer. Such claims also may lead consumers to believe that the product has benefits in treating or preventing disease, even if that is not the case.

Even if the remaining elements of the Central Hudson test are reached, the rule and the statutory provisions that it

implements are constitutional. As previously noted, this rule restricts no speech directly. Rather, it determines what types of speech in dietary supplement labeling will trigger other statutory provisions and regulations that may be considered restrictions on speech. To the extent that this rule, the statute, and the drug and health claim regulations restrict speech by requiring either health claim authorization or new drug approval before a business may make a disease claim for a dietary supplement, that restriction directly advances the substantial government interest in protecting and promoting the public health by helping to ensure that products intended to have an effect on a disease are safe and effective for that intended use. That interest is an interest both in preventing direct harm from such products--i.e., protecting the public from adverse events that such products might cause--and in preventing the indirect harm to health that is caused when an ill person foregoes medical care in favor of ineffective self-treatment.

Requiring prior FDA review and authorization of disease claims ensures that such claims will be evaluated by a public health agency that has scientific and medical expertise so that only products that are safe and effective will be permitted to be sold for therapeutic purposes. As a government agency with no financial stake in either permitting or denying claims, FDA is in

a position to evaluate the strength of the safety and efficacy evidence objectively.

The rule and the other components of the regulatory framework for drugs and health claims also advance the related substantial government interest in protecting consumers from fraud. If products are marketed for disease uses only after they have been demonstrated to be safe and effective for such uses, consumers will not suffer economic harm from spending money on worthless remedies.

Moreover, the rule is not more extensive than necessary. The agency does not believe that the alternatives mentioned in the comments, or any other alternative, would adequately further its substantial interest in protecting and promoting public health by ensuring the safety and efficacy of products intended to have an effect on disease. For example, allowing implicit disease claims, but not explicit ones, would merely allow companies to do indirectly what they cannot do directly--to market products for disease uses without demonstrating their safety and efficacy. Likewise, identifying specific terms that connote treatment, cure, or mitigation would not accomplish the goal of requiring proof of the safety and effectiveness of products marketed for disease uses. Merely regulating synonyms for those terms would leave unregulated those claims that achieve the same effect without using such a synonym, such as the claims

"herbal Prozac" and "for cancer." The suggestion in one comment that FDA establish "categories of diseases that clearly denote drug claims" is not a workable alternative either. Section 403(r)(6) of the act provides that the category of structure/function claims excludes claims to affect any category of disease, not just certain categories.

Permitting disease claims under section 403(r)(6) of the act as long as they are accompanied with a disclaimer, as suggested by the comment that cited the *Pearson* decision, would be an untenable alternative. If companies could avoid the time and expense of complying with the new drug provisions of the act merely by attaching a disclaimer to a disease treatment or prevention claim, the longstanding system of drug regulation in this country would be eviscerated, with serious public health consequences. Nothing in Pearson requires such a result. Indeed, the Pearson court recognized that its ruling did not apply to drugs (164 F.3d at 656 n. 6). Because the act classifies products on the basis of intended use, dietary supplements that make disease claims are drugs, unless the disease claim is also an authorized health claim for which the product qualifies (see section 201(g)(1) of the act).

The Washington Legal Foundation decision is not to the contrary. That case involved the dissemination of information on "off-label" (unapproved) uses for approved drugs and devices to

physicians by means of scientific and educational symposia, reprints, and textbooks. The U.S. District Court for the District of Columbia held certain FDA guidance documents that described acceptable ways of disseminating such information unconstitutional under the Central Hudson test. While recognizing the substantial government interest in having off-label uses for drugs and devices found to be safe and effective by FDA, the court held that the guidance documents violated the First Amendment because it believed that they "restricted" speech in a manner that was more extensive than necessary to further that interest. (See 13 F. Supp. 2d at 73.) (Subsequent to the 1998 decision cited by the comments, the court rendered another decision adverse to FDA (Washington Legal Foundation v. Henney, 1999 WL 557679 (D.D.C. July 28, 1999)). That decision concerned the constitutionality of certain provisions of the FDA Modernization Act of 1997 involving the same subject matter as the guidance documents, and the court's First Amendment rationale was similar to its rationale in the 1998 decision pertaining to the guidance documents.)

FDA disagrees with the district court decision in Washington Legal Foundation and has appealed. In any event, however, the outcome in Washington Legal Foundation does not determine the outcome here for several reasons. First, in Washington Legal Foundation the court found a less restrictive alternative that it

concluded would more precisely address the government's regulatory concerns: Requiring manufacturers who disseminate information about off-label uses to physicians through scientific reprints or educational symposia to disclose: (1) Their interest in drugs or devices that are the subject of such activities, and (2) the fact that the use discussed has not been approved by FDA. Here, as explained previously, there are no less restrictive alternatives to this rule that would further the government's substantial public health interest. Second, in Washington Legal Foundation physicians were the intended audience of the commercial speech at issue. In contrast, consumers are the primary audience for dietary supplement labeling. Although the marketplace includes consumers of varying levels of sophistication, the average consumer does not possess the medical and scientific expertise necessary to evaluate claims about the effect of a product on disease. (See American Home Products Corp. v. FTC, 695 F.2d 681, 698 (3d Cir. 1983); Association of Nat'l Advertisers, Inc. v. Lungren, 44 F.3d 726, 733-34 (9th Cir. 1994), cert. denied, 516 U.S. 812 (1995).) Finally, in Washington Legal Foundation, it was undisputed that the products involved were drugs (or, in some cases, devices) to be used in treating or preventing disease. In contrast, the purpose of this rule is to distinguish between products that are intended to affect disease and products that are not.

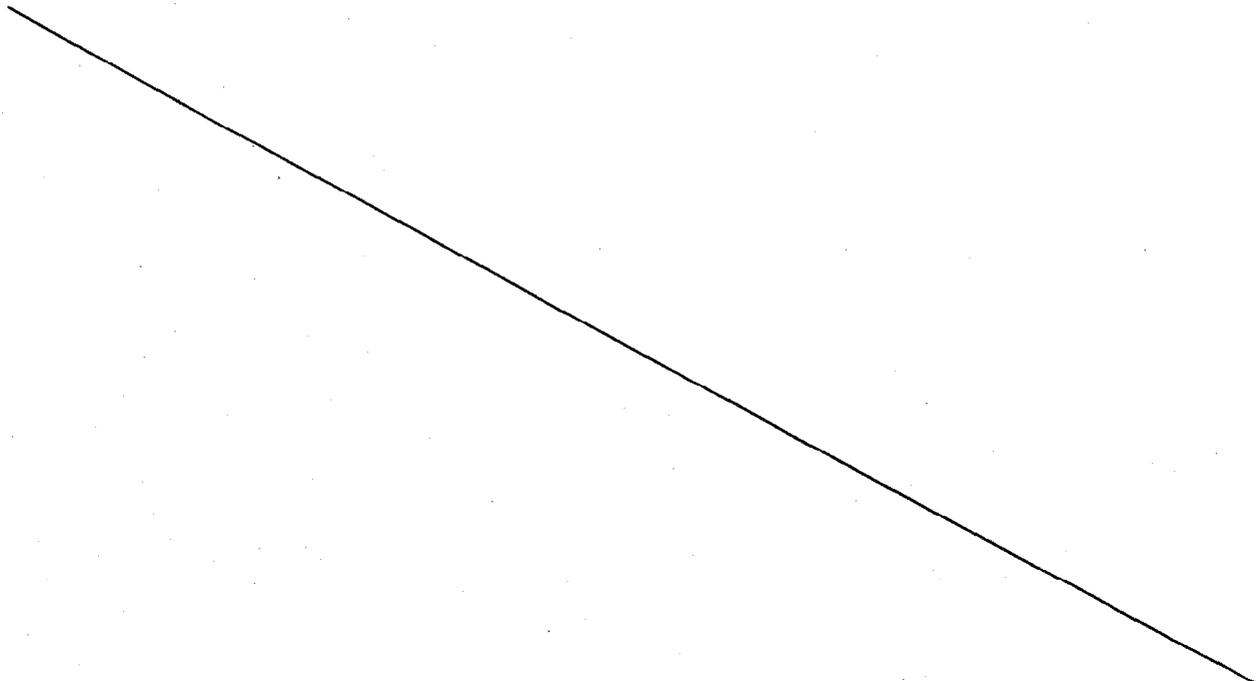
The agency does not believe this rule is premature in light of the need to reassess the regulatory regime for health claims under *Pearson*. Since health claims and structure/function claims are regulated separately, there is no need to wait for any post-*Pearson* changes for health claims to be complete before proceeding with this rulemaking on structure/function claims. Moreover, since the agency has decided not to amend the health claims regulations as part of this rulemaking, there is no potential conflict between the two.

The First Amendment issues raised in comments on § 101.93(g)(4)(iii) (proposed § 101.93(g)(2)(iv)(C)), concerning citations to scientific references in labeling, are not different from those raised by comments on the rule as a whole and are addressed in the preceding analysis. FDA also notes that, as discussed elsewhere in this document, § 101.93(g)(4)(iii) has been revised to narrow the circumstances under which the agency will consider citations to scientific references in labeling to be disease claims.

(109.) Another comment further asserted that the prohibition against implied disease claims violates the First Amendment because it does not advance the safety of dietary supplements. The comment acknowledged that some dietary supplements "may present serious safety risks," but said "these risks will not be lessened by prohibiting truthful, non-misleading structure/function

claims * * *." The comment suggested that other provisions in DSHEA address the safety of dietary supplements and that FDA can bring an enforcement action if it has safety concerns.

FDA agrees with this comment in part and disagrees in part. The agency agrees that prohibiting truthful, non-misleading structure/function claims would not lessen the safety risks posed by some dietary supplements. The rule is aimed at the safety risks posed by unapproved drug claims and unauthorized health claims on dietary supplements. Unproven disease claims on a product marketed as a dietary supplement may induce consumers to treat themselves with the supplement instead of seeking treatments that are known to be effective. Such claims may also dissuade consumers from seeing a doctor. These are very real safety risks. To the extent that safety risks are caused by the composition of a dietary supplement rather than by claims made for it, the agency agrees that other provisions in DSHEA and the act are the appropriate remedy.



2. Equal Protection

(110.) One comment claimed the rule violates the equal protection clause of the Fourteenth Amendment because it supposedly gives more protection to the "labeling rights and speech" of pharmaceutical manufacturers than to dietary supplement manufacturers.

First, it should be noted that the equal protection clause of the Fourteenth Amendment applies only to the States, not to the Federal Government. However, the due process clause of the Fifth Amendment contains an equal protection component that is equivalent to the equal protection clause of the Fourteenth Amendment (Schweiker v. Wilson, 450 U.S. 221, 226 & n. 6 (1981)). Even if the comment is interpreted to refer to equal protection under the Fifth Amendment, FDA disagrees with it. First, the comment does not explain in what manner the rule gives more protection to the labeling rights and speech of pharmaceutical manufacturers than to those of dietary supplement manufacturers. Second, even if the rule does treat these two classes of manufacturers differently, treating different regulated groups differently does not in itself violate the equal protection clause. Unless a regulatory classification jeopardizes the exercise of a fundamental right or classifies upon inherently suspect grounds such as race or religion, it is subject to the least exacting form of equal protection review: Whether the

classification it draws bears a rational relationship to a legitimate government interest. (See Nordlinger v. Hahn, 505 U.S. 1, 10 (1992).)

This rule neither jeopardizes the exercise of a fundamental right nor creates a suspect classification. The purpose of the rule is to clarify the statutory distinction between products that are intended for use in treating or preventing disease and products that are intended for use in affecting the structure or function of the body. Products intended to treat or prevent disease are subject to regulation as drugs, unless they qualify for an authorized health claim. Products intended to affect the structure or function of the body may be regulated as dietary supplements, subject to certain conditions. Products regulated as drugs must meet strict requirements for a premarket demonstration of safety and efficacy (see sections 201(p) and 505 of the act); these requirements do not apply to dietary supplements. The distinction that the statute and this rule draw between products that are intended to have an effect on disease and those that are intended only to affect the structure or function of the body is clearly rationally related to the legitimate government interest of ensuring that products intended to have an effect on a disease are safe and effective for that intended use.

3. Takings Under the Fifth Amendment

(111.) Several comments claimed that the proposal violates the Takings Clause of the Fifth Amendment because it would prohibit the use of specific terms that now appear in product names, trademarks, trade names, symbols, and company logos, or would harm companies that use such terms in their corporate names. One comment said FDA must provide compensation for each taking, but that the proposal failed to do so.

FDA disagrees with these comments. The Takings Clause forbids the government from taking private property for public use without just compensation. However, FDA believes that no taking will occur as a result of this rule.

The first issue to be considered is whether the categories of names, words, and symbols identified in the comments on this issue are property within the meaning of the Takings Clause. The Constitution itself does not define what qualifies as property. Rather, "existing rules or understandings derived from an independent source," such as State or Federal law, define the interests that qualify for protection as property under the Fifth Amendment (Lucas v. South Carolina Coastal Council, 505 U.S. 1003, 1030 (1992)).

The categories of names, words, and symbols mentioned by the comments are intangible property interests. As discussed below, trademarks and trade names are property to the extent that they are associated with business goodwill. A trademark is a word,

name, symbol, device, or combination thereof that a person uses, or intends to use and has applied to register, to identify and distinguish his or her goods from others on the market and to indicate their source (15 U.S.C. 1127). A trade name is the name a person uses to identify his or her business (15 U.S.C. 1127) and may include corporate, partnership, and other names. Symbols and logos, when used to identify a product or company, may be property insofar as they are trademarks or trade names.

Likewise, product names may be property if they are protected by a trademark or trade name. For brevity, in the remainder of this discussion the categories of names, words, and symbols mentioned by the comments on the takings issue will be referred to collectively as "trademarks and trade names."

Trademarks and trade names are property, but only insofar as they are associated with the goodwill of an ongoing business. (See American Steel Foundries v. Robertson, 269 U.S. 372, 380 (1926).) They have no intrinsic value. The purpose of a trademark or trade name is to prevent confusion with the products of another manufacturer. (See United Drug Co. v. Theodore Rectanus Co., 248 U.S. 90, 97 (1918).) Trademarks and trade names are given legal protection to prevent one manufacturer from passing off its goods as the goods of another and thus taking advantage of the latter's goodwill (American Steel Foundries, 269 U.S. at 380; United Drug, 248 U.S. at 97).

The Supreme Court has declined to prescribe a "set formula" for identifying takings and instead has characterized takings analysis as an "essentially ad hoc, factual" inquiry (Penn Central Transp. Co. v. City of New York, 438 U.S. 104, 124 (1978)). Nonetheless, the Court has identified three factors for consideration in assessing whether a regulatory taking has occurred: The character of the governmental action; the regulation's economic impact; and the extent to which the regulation interferes with reasonable investment-backed expectations (Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1005 (1984)). The force of any one of these factors may be "so overwhelming * * * that it disposes of the taking question" (Monsanto, 467 U.S. at 1005). When examined in light of these three factors, the rule does not effect a compensable taking under the Fifth Amendment.

a. The character of the government action. With respect to the first factor, the character of the government action, courts are more likely to find a taking when the interference with property can be characterized as a physical invasion by government than when the interference is caused by a regulatory program that "adjust[s] the benefits and burdens of economic life to promote the common good" (Penn Central, 438 U.S. at 124). The Supreme Court has held that, when a governmental action is taken in order to protect the public interest in health, safety, and

welfare, this factor weighs heavily against finding a taking. (See Keystone Bituminous Coal Ass'n v. DeBenedictis, 480 U.S. 470, 488 (1987).) Regulatory actions taken to protect the public health are rarely, if ever, held to constitute takings. (See Porter v. DiBlasio, 93 F.3d 301, 310 (7th Cir. 1996) (action taken to protect public health falls within class of property deprivations for which Fifth Amendment does not require compensation); Jarboe-Lackey Feedlots, Inc. v. United States, 7 Cl. Ct. 329 (1985) (seizure of adulterated meat not a taking).)

Although these regulations will restrict the use of certain terms, including terms that appear in some trademarks and trade names, this restriction does not rise to the level of a taking. Governmental restrictions on the uses individuals can make of their property are "properly treated as part of the burden of common citizenship" (Keystone, 480 U.S. at 491 (citation omitted)). These burdens are "borne to secure 'the advantage of living and doing business in a civilized community'" (Andrus v. Allard, 444 U.S. 51, 67 (1979) (quoting Pennsylvania Coal Co. v. Mahon, 260 U.S. 393, 422 (1922) (Brandeis, J., dissenting))). Moreover, these regulations are not without benefit to manufacturers. (See Keystone, 480 U.S. at 491 ("While each of us is burdened somewhat by such restrictions, we, in turn, benefit greatly from the restrictions that are placed on others.")) The regulations will help ensure a level playing field in the dietary

supplement market because no manufacturer will be able to make an implied disease claim without prior FDA review under the health claim or new drug standard. Previously, unreviewed implied disease claims on dietary supplements proliferated, in part because of uncertainty about the line between structure/function claims and disease claims.

These regulations are rationally related to, and substantially advance, FDA's legitimate interest in promoting and protecting the public health by ensuring the safety and efficacy of products promoted for use in treating or preventing disease. (See Keystone, 480 U.S. 470 at 485; Monsanto, 467 U.S. at 1007.) By clarifying that such products may not be marketed under the structure/function claim regime, FDA is seeking to ensure that they are regulated through the drug approval or health claims authorization process, as appropriate.

The effect of the regulations cannot be characterized as a taking of property. Dietary supplement companies will not be precluded from using terms that imply a disease claim in their trademarks and trade names. If they wish to continue using trademarks and trade names that imply a disease claim, they may do so, provided that they first meet the safety and efficacy standards and other regulatory requirements applicable to drugs or, in appropriate cases, provided that they obtain authorization

to make a health claim. (As discussed below, only non-misleading trademarks and trade names may be used.)

Even if these regulations could be said to prevent a business from using a trademark or trade name on its dietary supplements, such a result still would not constitute a taking of the trademark or trade name. The purpose of giving trademarks and trade names legal protection is to prevent one manufacturer from passing off its goods as the goods of another (American Steel Foundries, 269 U.S. at 380). This regulation will not allow one manufacturer to use another's trademark or trade name; rather, all manufacturers will be precluded from using trademarks and trade names that contain an implied disease claim unless they have obtained new drug approval or health claim authorization. Thus, manufacturers will not suffer any competitive injury.

Moreover, deprivation of a trademark alone is not a deprivation of property. Because the trademark is "merely a protection for the good will" (Hanover Star Milling Co. v. Metcalf, 240 U.S. 403, 414 (1916)), only if a regulation takes the owner's goodwill as well would the regulation be a taking. It is not apparent, however, that these regulations will deprive manufacturers of any goodwill. Manufacturers will be faced with a choice as to whether to change their trademark or trade name or to seek approval for their products as drugs. In some cases, they will also have a third option: Seeking authorization to

make a health claim. If they are able to obtain drug approval for the intended use suggested by the trademark or trade name, they will not have to change the trademark or trade name, provided that the name is not confusingly similar to the name of another drug or otherwise misleading (see section 502(a)(1) of the act (21 U.S.C. 352(a)(1)); and § 201.10(c)(3) and (c)(5).) Similarly, if they are able to obtain authorization to make a health claim for the intended use suggested by the trademark or trade name, they will not have to change the trademark or trade name unless it is misleading. (See section 403(a)(1) of the act.) Even if a manufacturer chooses to change its trade name or trademark, it will not be deprived of the goodwill underlying them but only of that particular symbol of the goodwill. The manufacturer will still be able to transfer the goodwill associated with its products to another trade name or trademark.

Case law on the treatment of goodwill under the Takings Clause supports the view that no taking will occur as a result of these regulations. The general rule is that the owner of a place of business to which the government takes title is not entitled to compensation for loss of goodwill (United States v. General Motors Corp., 323 U.S. 373, 379 (1945)). The reason for the rule is that the business may reopen at another location to which the goodwill may be transferred (Kimball Laundry Co. v. United States, 338 U.S. 1, 11-12 (1949)). Only where the government

operates the business, thereby depriving the owner of its "going-concern value," is there a compensable taking of goodwill. In Kimball, the Supreme Court held that the government owed compensation for the loss of goodwill associated with the temporary taking of a laundry during World War II. This action was held to be a taking of goodwill because the government not only physically took but also operated the laundry during the war (Kimball, 338 U.S. at 12-13). Thus, during the period that the government operated the laundry, there was no business to whose benefit the goodwill associated with the private laundry business could inure. Here, the government is not taking any trademark or trade name for its own use, nor is it shutting down the businesses that own them. Therefore, the goodwill symbolized by the trademark or trade name will remain with these businesses.

Finally, although trademarks and trade names can be property when they symbolize and protect the goodwill associated with a business, there can be no property interest in an illegal product. Dietary supplements that bear claims to treat or prevent disease are misbranded and are also unapproved new drugs (unless the claim is an authorized health claim). As such, they may not legally be sold in interstate commerce (see section 301 (a) and (d) of the act. There can be no taking of an illegal article. (See Meserey v. United States, 447 F. Supp. 548, 554 (D. Nev. 1977) ("Plaintiff has not been denied his property. He

is denied the right to introduce his goods into commerce unless they are in compliance with the [Federal Food, Drug, and Cosmetic] Act.".) Moreover, it has always been illegal to market dietary supplements or other foods with disease claims, except that since 1990 the act has permitted authorized health claims. These regulations merely clarify the line between acceptable structure/function claims and prohibited disease claims. (See Lucas, 505 U.S. at 1030 ("The use of [property] for what are now expressly prohibited purposes was always unlawful, and * * * it was open to the State at any point to make the implication of those background principles of * * * law explicit" without paying compensation) (emphasis in original).) For this reason and the other reasons previously discussed, the first factor of the takings analysis indicates that these regulations effect no takings.

b. The economic impact of the government action. The second factor to consider is the economic impact of the government action. This impact is not to be considered piecemeal by dividing a property interest "into discrete segments and attempt[ing] to determine whether rights in a particular segment have been entirely abrogated" (Penn Central, 438 U.S. at 130). The analysis involves looking not just at what has been lost, but at the nature and extent of the interference with rights in the property as a whole. (See Penn Central, 438 U.S. at 130-31;

Andrus v. Allard, 444 U.S. at 65-66.) Thus, here the total impact of the regulations on property rights should be considered, rather than only whether a business can or cannot continue to use a particular trademark or trade name. It is clear that a regulation's economic impact may be great without rising to the level of a taking. (See Pace Resources, Inc. v. Shrewsbury Township, 808 F.2d 1023, 1031 (3d Cir.), cert. denied, 482 U.S. 906 (1987) (citing Hadacheck v. Sebastian, 239 U.S. 394 (1915) (reduction in value from \$800,000 to \$60,000); Euclid v. Ambler Realty Co., 272 U.S. 365 (1926) (75 percent diminution in value)).)

In assessing whether a regulation effects a taking, the Supreme Court has considered whether the regulation denies an owner the "economically viable" use of its property. (See, e.g., Keystone, 480 U.S. at 499.) Although it is undeniable that compliance with these regulations will cost money and may mean that certain trademarks and trade names must be altered, companies will not be denied the economically viable use of their property. As previously discussed, some firms may be able to obtain new drug approval or health claim authorization for those products that bear trademarks or trade names that include disease claims. If approved as new drugs or authorized to bear a health claim, in many cases these products could continue to bear the original trademark or trade name. This approach would, however,

require the company involved to make significant expenditures of time and money to submit a new drug application (NDA) or health claim petition to FDA. The financial burden required to comply with such requirements is not a taking under these circumstances, however, just as it is not a taking to require other companies to comply with applicable requirements before marketing a new drug or a food bearing a health claim. Obtaining new drug approval or authorization to make a health claim may be costly, but it is not the kind of economic impact that leads to a taking. "Requiring money to be spent is not a taking of property" (Atlas Corp. v. United States, 895 F.2d 745, 756 (Fed. Cir.), cert. denied, 498 U.S. 811 (1990)).

As previously noted in the discussion of the first factor of the takings analysis, case law indicates that the regulations will cause no loss of goodwill even in cases where a trademark or trade name must be changed because new drug approval or health claim authorization cannot be obtained. Even if the regulations do cause a loss of goodwill, however, FDA believes that the economic impact of that loss of goodwill is outweighed in the takings analysis by lack of reasonable investment-backed expectations in being able to make disease claims in trademarks and trade names.

c. Interference with reasonable investment-backed expectations. The final factor to consider is whether a company has a reasonable investment-backed expectation in continuing to use a trademark or trade name. To be reasonable, expectations must take into account the power of the state to regulate in the public interest (Pace Resources, 808 F.2d at 1033). Reasonable expectations must also take into account the regulatory environment, including the foreseeability of changes in the regulatory scheme. "In an industry that long has been the focus of great public concern and significant government regulation," Monsanto, 467 U.S. at 1008, the possibility is substantial that there will be modifications of the regulatory requirements. "Those who do business in the regulated field cannot object" if the regulatory scheme is "buttressed * * * to achieve the legislative end" (Connolly v. Pension Benefit Guar. Corp., 475 U.S. 211, 227 (1986) (citation omitted)). The lack of a reasonable investment-backed expectation can outweigh the other takings factors and be determinative in whether a taking has occurred (Monsanto, 467 U.S. at 1005).

Companies that use trademarks or trade names that include disease claims lack a reasonable investment-backed expectation that they will be able to continue to use those trademarks and trade names. First, the Supreme Court has said that it is unreasonable to have high expectations in personal property

(i.e., property other than land): "[I]n the case of personal property, by reason of the State's traditionally high degree of control over commercial dealings, [the property owner] ought to be aware of the possibility that new regulation might even render his property economically worthless * * *." (Lucas v. South Carolina Coastal Council, 505 U.S. at 1027-28). Second, the dietary supplement and drug industries are a "focus of great public concern and significant government regulation" (Monsanto, 467 U.S. at 1008). A product that bears a disease claim, whether that claim appears in a trademark, trade name, or elsewhere, has been subject to regulation as a drug since 1906, except that since 1990 the act has permitted conventional foods and dietary supplements to bear authorized health claims without drug approval. Since 1938, drugs (with certain narrow exceptions) have been subject to a premarket approval requirement. Given this longstanding history of close regulation, it cannot be reasonable for a manufacturer or distributor to expect to be able to make disease claims without prior authorization from FDA.

Moreover, it has always been illegal to market dietary supplements or other foods with disease claims, except that since 1990 authorized health claims have been permitted. These regulations merely clarify the line between acceptable structure/function claims and prohibited disease claims. (See Lucas, 505 U.S. at 1030 ("The use of [property] for what are now

expressly prohibited purposes was always unlawful, and * * * it was open to the State at any point to make the implication of those background principles of * * * law explicit.".) Companies in the dietary supplement industry should have been aware that FDA was likely to issue such a clarification, not only because of the regulatory environment generally but also for several specific reasons. First, the passage of DSHEA, which added section 403(r)(6) to the act, created a likelihood that FDA would issue regulations "to achieve the legislative end" of permitting structure/function claims without premarket review, while continuing to prohibit disease claims lacking FDA authorization (see Connolly, 475 U.S. at 227 (citation omitted)). Second, the Commission on Dietary Supplement Labels specifically encouraged FDA to clarify the appropriate scope of structure/function statements (Ref. to Commission report, p. 38). Third, the rapidly expanding dietary supplement market and the proliferation of implied disease claims in labeling should have put the industry on notice that FDA might take action.

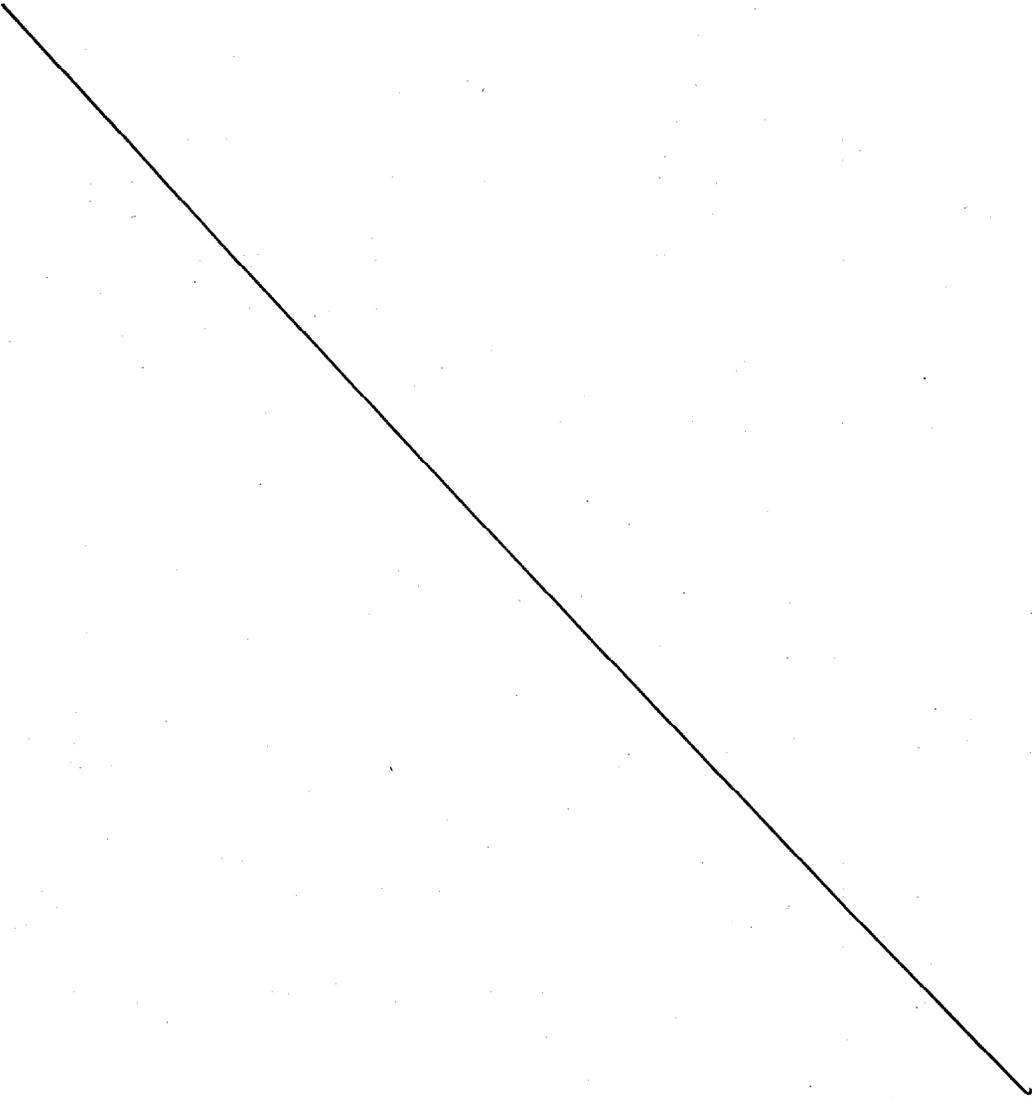
For all these reasons, there can be no reasonable investment-backed expectations with respect to trademarks and trade names that include disease claims. Thus, the third factor of the takings analysis weighs strongly against finding a taking of property that requires compensation under the Fifth Amendment. Moreover, the three factors, taken together, show that these

regulations do not effect such a taking. Therefore, FDA concludes that the comments arguing the contrary are unpersuasive.

IV. Implementation Plan

The preamble to the proposed rule discussed FDA's tentative conclusions regarding the effective date of a final rule and the agency's implementation plan. In general, the preamble to the proposed rule stated that a final rule would become effective 30 days after the date of the final rule's publication in the FEDERAL REGISTER. Any product that is marketed for the first time after publication of the final rule, and any new claims made for an existing product for the first time after the publication of the final rule, will be expected to be in compliance beginning 30 days after publication of the final rule. However, small businesses that marketed a product as of the date of publication of a final rule would have had an additional 17 months to bring existing claims (i.e., claims already in the product's labeling on [Insert date of publication in the FEDERAL REGISTER]) for those products into compliance, provided that the small business had notified FDA of the claim as required by section 403(r)(6) of the act and § 101.93(a) and that FDA had not objected to the claim. For all other products that were on the market as of the date of publication of a final rule, FDA would have allowed an additional 11 months beyond the effective date to bring existing claims for those products into compliance, provided that the firm

had notified FDA of the claim as required by section 403(r)(6) of the act and § 101.93(a) and that FDA had not objected to the claim. Any product marketed for the first time after the date of publication of the final rule, and any new claim made for an existing product for the first time after publication of the



final rule, would have been expected to be in compliance beginning 30 days after the date of publication of a final rule.

(112.) Two comments suggested extending the compliance period to 6 months after the date of publication of a final rule. The comments also advocated that there be no distinction between large and small businesses for compliance dates. The comments further suggested that FDA give businesses whose products were on the market as of the date of publication of a final rule 15 months (instead of 11 or 17 months) to comply. Another comment suggested that the final rule become effective 12 months, rather than 30 days, after its publication date.

FDA believes that the proposed compliance periods of 11 and 17 months following the effective date of the final rule are reasonable and fair, and that the distinction between large and small businesses is appropriate. FDA has decided, however, that it will not treat manufacturers who have not notified the agency of their claims differently from other manufacturers. At least some of those manufacturers who did not submit 30-day notifications to the agency may have failed to do so believing that notification was not necessary under section 201(g)(1)(C) of the act. Therefore, all manufacturers will have 11 months after the effective date of the final rule to come into compliance, and small businesses will have 17 months after the effective date of the final rule. The agency believes that these compliance

periods, uniformly applied, are sufficiently long that it is not necessary to extend the effective date to 6 months after publication in the FEDERAL REGISTER.

For a limited transition period, FDA does not intend to take enforcement action against firms who have relied on the agency's September 1997 preamble statements to make a structure/function claim for a dietary supplement under section 201(g)(1)(C) of the act. To allow a reasonable time for the necessary label changes, the transition period will last until the applicable compliance date for the rest of the rule; i.e., small businesses will have 18 months from publication to comply, and other firms will have 12 months. As of the applicable compliance date, firms that have been making structure/function claims under section 201(g)(1)(C) must either remove the claim or comply with the requirements of section 403(r)(6) of the act and § 101.93, including notifying FDA of the claim and relabeling to add the required disclaimer. New structure/function claims are not subject to this transition period; any firm that makes a structure/function claim in the labeling of a dietary supplement after the effective date of this rule must comply with section 403(r)(6) of the act and § 101.93.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) and (k), that this action is of a type that does not individually or cumulatively have a significant effect on the human environment.

Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Analysis of Impacts

A. Background

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to examine the economic impact of a rule on small entities. The Unfunded Mandates Reform Act requires agencies to prepare an assessment of anticipated costs and benefits before enacting any rule that may result in an expenditure in any one year by State, local and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

FDA concludes that this final rule is consistent with the principles set forth in the Executive Order and in these two statutes. The agency has determined that the rule is a significant regulatory action as defined by the Executive Order,

because it raises novel policy issues. FDA has further determined that the final rule may have a significant economic impact on a substantial number of small entities. This section constitutes the agency's final regulatory flexibility analysis as required under the Regulatory Flexibility Act. Because this rule imposes no mandates on government entities and will not result in private expenditures of \$100 million in any one year, the Unfunded Mandates Reform Act does not require the agency to prepare a cost-benefit analysis.

B. Benefits of the Labeling Requirements

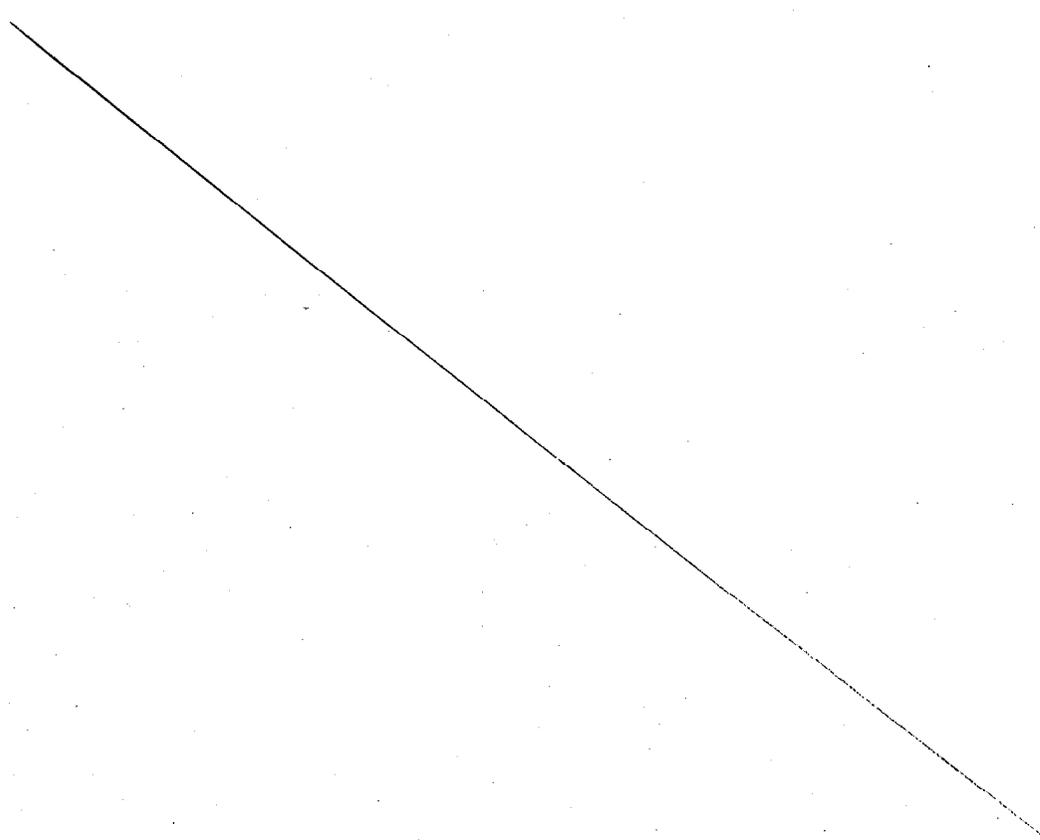
The primary purpose of the rule is to provide a consistent standard for distinguishing between claims that may be made in labeling without prior review by FDA and claims that require prior authorization as health claims or prior review as drug claims. The larger goal is to ensure that information about non-disease-related effects of a dietary supplement on the body may be freely disseminated in labeling, while at the same time guaranteeing that claims for use of a dietary supplement to treat or prevent disease are not made without prior review to ensure that the supplement is safe and effective for that use.

Although dietary supplements can play a valuable role in consumer health, the agency recognizes that, when inappropriately labeled, they can pose unnecessary risks. Such risks arise when the product labeling: (1) Encourages consumers to self-treat

for a serious disease without the benefit of a medical diagnosis, or to self-treat for a serious disease by substituting a dietary product of uncertain value for a medical therapy that has been shown to be safe and effective; (2) encourages consumers to feel sufficiently protected from a serious disease (e.g., cancer) that they delay, or possibly forego, regular screening or early medical attention that may be critical to improved odds of patient survival; or (3) increases the risk of adverse reactions due to interactions with other chemical compounds (e.g., prescription medications) taken by the patient. As consumer spending on dietary supplements continues to rise, the need for an information standard that minimizes these risks becomes more acute.

The rule may also benefit consumers by encouraging manufacturers of dietary supplements to develop the safety and effectiveness data needed to support a health or drug claim. Where disease claims can be made without this demonstration of safety and effectiveness, product manufacturers have less incentive to develop the substantial documentation needed to receive this agency authorization. The availability of additional products with authorized health or drug claims would be extremely useful to the many consumers who have difficulty distinguishing among the variety of products now marketed for particular health concerns.

The dietary supplement industry has grown rapidly, with estimated sales in 1996 of \$10.4 billion for all dietary supplements, including \$4.9 billion for vitamins and \$3.0 billion for nonprescription herbal products (Ref. 8). FDA has limited information on the number of products and quantities sold, or on the age, gender, and disease status of persons currently using dietary supplements. However, a 1997 survey of 43,000 households, conducted by the Hartman and New Hope research organization, indicates that approximately 70 percent of all households reported using vitamins, minerals, or herbal supplements in the past 6 months (Ref. 9). Among survey



respondents, those under age 30 accounted for only 8 percent of all households with a member using dietary supplements; ages 30 to 39 accounted for 21 percent, ages 40 to 49 accounted for 22 percent, ages 50 to 59 accounted for 18 percent, and ages 60 or older accounted for 30 percent (Ref. 10). Although the oldest group of survey respondents were, on the whole, less knowledgeable about individual products, they reported more regular product use and more use for specific conditions than younger respondents.

FDA anticipates, therefore, that the final rule will clarify the dividing line between acceptable structure/function claims and disease claims, and thereby reduce the number of inappropriate disease claims in dietary supplement labeling. The defined standard for structure/function claims under section 403(r)(6) of the act will help to avoid instances of inappropriate substitution of dietary products for timely disease screening or medical treatment, and of adverse interactions or contraindications of drug-supplement combinations. In addition, the rule may promote the development of data and information for the support of new health or drug claims. Although FDA cannot quantify these regulatory benefits, the agency expects that this standard will positively support the effective integration of dietary supplements into consumers' overall programs of wellness and self-care.

C. Costs of Compliance

The costs to industry are the direct costs of compliance, which are primarily the costs of the needed product relabeling; and the indirect costs of compliance, which include the potential loss of product sales due to the elimination of disease claims. The following section details the agency's calculation of the direct costs of compliance. FDA has been unable, however, to estimate the extent of the indirect costs of this rule. As explained below, the agency estimates that over 800 dietary supplement products will need to be relabeled due to this rule. The substitution of a valid structure/function claim for a disease claim may, in fact, lead to a decrease in the sale of certain products. The magnitude of this impact, however, is unknown, as most firms will replace the disease claim with a structure/function claim that appeals to many of the same consumers. It is also possible that some firms will avoid a potential drop in sales by developing the safety and effectiveness data needed to obtain either a new drug approval or authorization from FDA to make a health claim. The agency cannot quantify the probability of these occurrences, however, and no industry comment includes such data.

1. Proposed Rule

In the preamble to the proposed rule (63 FR 23624), FDA had projected that the direct costs of compliance would range from \$0.1 million to \$8.5 million. This figure largely reflected agency estimates of the average cost of relabeling a typical dietary supplement product multiplied by the number of dietary supplement products that would need to be relabeled to conform with the proposed criteria for structure/function claims. The cost categories included administrative, analytical, and inventory disposal activities.

FDA acknowledged that estimates of the number of dietary supplement products were approximate, but projected that the proposed rule would cover about 29,000 products, with about 75,000 distinct labels, or stock keeping units (SKU's). The agency also explained that the rule would directly affect from 500 to 850 manufacturers of dietary supplement products.

To estimate the lower-bound costs of the proposed rule, FDA assumed that the 2,300 notifications initially received from dietary supplement manufacturers adequately represented the number of products with structure/function claims. The agency had already objected to 150 notifications because they contained obvious disease claims, but identified an additional 60 notifications containing one or more claims that might not have met the newly proposed criteria for structure/function claims. Consequently, FDA's lower-bound direct cost estimate included

label changes for 60 dietary supplement products. The estimated administrative, redesign, and inventory losses associated with these 60 label changes totaled between \$91,400 and \$123,400.

FDA also presented an upper-bound \$8.5 million estimate of the direct costs of the proposed rule, based on the likelihood that many additional dietary supplements are marketed with structure/function claims. For this estimate, the agency concluded that about 30 percent, or 22,500, of the estimated universe of 75,000 dietary supplement labels contain structure-function claims. Assuming that the proportion of disease claims on all labels containing structure/function claims equals the proportion of disease claims in the 2,300 notifications containing structure/function claims, the agency calculated that up to 585 labels ($60/2,300 \times 22,500$) could need to be changed if the proposed rule became final. The higher costs of the upper-bound estimate resulted both from the substantially increased assumed number of affected labels and from the impact of the significantly shorter compliance period (30 days) for manufacturers that had not notified FDA of their structure/function claim by the publication date of the final rule.

2. Final Rule

A number of the comments submitted in response to the proposed rule specifically addressed FDA's analysis of compliance

costs. As a result, the agency has altered several of its cost assumptions. In addition, FDA has adjusted its analysis to reflect the modified provisions of the final rule. As described below, the agency estimates the total direct costs of the final rule to be about \$3.73 million, but presents sensitivity analysis to indicate that the costs could rise to as much as \$10.35 million under certain worst-case assumptions.

Although several industry comments suggested that FDA had underestimated the costs of relabeling, no comments objected to the specific elements that were considered, i.e., administrative, redesign, and inventory disposal activities. In response, FDA has retained this format for its analysis of the final rule. One comment claimed that FDA had underestimated the number of products that would be affected, but provided no evidence or basis for determining a more accurate count. Another comment stated that the agency's cost estimates were not well explained and that all assumptions were not disclosed. Consequently, FDA has revised its analysis to; (1) Simplify the cost-estimating methodology, (2) clearly present and describe each assumption, (3) fully explain the derivation of the estimated direct costs of compliance, and (4) conduct sensitivity analysis for the remaining areas of significant uncertainty.

a. Cost of designing new labels. Dietary supplements will no longer be able to make claims whose status was previously

unclear, but which now have been defined as disease claims. Firms may comply either by obtaining new drug approval, by receiving authorization from FDA to make a health claim, or by revising their product labeling to eliminate disease claims. Because the cost of submitting adequate documentation to obtain new drug approval or health claim authorization far exceeds the cost of modifying a label, this analysis assumes that the direct costs of the rule will be the costs of modifying labels with disease claims. As explained above, FDA recognizes that some firms may choose to obtain health claim authorization or new drug approval as an alternative means of compliance, or to improve the marketability of their products. The agency believes, however, that it is unlikely that the rule would be the determining factor in a large number of instances.

No public comments provided alternative estimates of the number of affected dietary supplement products. As noted above, FDA had estimated that the industry markets approximately 29,000 covered products with about 75,000 distinct labels. The agency has used this estimate for its analyses of dietary supplement rules over the past several years (e.g., 60 FR 67211, December 28, 1995) and has received no indication from industry that better estimates were available. Although the agency's preliminary analysis reported that an estimated 30 percent of the products (8,700) carry structure/function claims, more recent data from a random survey conducted for FDA by RTI of about 3,000

dietary supplement products indicates that this percentage may have been too low (Ref. 11). Although RTI notes that the surveyed sample is too small to support quantitative inferences for the population of dietary supplements, FDA finds the data to be the best available. The RTI report actually shows that 69 percent of the products in its sample have claims, but this percentage includes "diet supplementation" claims. When adjusted to exclude "diet supplementation" claims, only 62 percent of the products in the RTI data base include relevant claims. Even this 62 percent figure is too high, however, because RTI over-sampled herbal products, which have a higher probability of claims. Thus, FDA believes that the true percentage of dietary supplement products with claims would not exceed 60 percent and has used this figure as its final estimate.

Of the first 2,300 notifications of structure/function claims reviewed by FDA, no more than 60, or 2.6 percent of the products with claims, would have needed labeling changes due to the criteria described in the proposed rule. Since that time, the total number of notifications with structure/function claims submitted to the agency has increased to about 4,350. A subsequent review of all of the submitted claims indicates that the final rule could require 1.9 times as many label modifications as the proposed rule, owing largely to the revised criteria for cholesterol claims in the final rule. FDA

estimates that the final rule may require revised labels for about 4.81 percent of the 17,400 dietary supplement products (29,000 x 60%) currently estimated as marketed with structure/function claims (Refs. 15 and 16). (Excluding cholesterol claims would reduce this figure to 1.74 percent of the products with claims.)

The resulting label cost calculations are straightforward. First, the agency found that revised labels (for all claims including cholesterol) may be needed for approximately 837 products (17,400 products with claims x 4.81 percent). Because each product may contain roughly 2.6 distinct SKU's (75,000 SKU's ÷ 29,000 products), labels for an estimated 2,164 SKU's may need to be modified (837 products x 2.6 SKU's/product). As described in its earlier analysis, based on an average of the estimates provided in comments to earlier rules, FDA determined that the average label redesign cost is about \$1,700 per dietary supplement SKU for a 12-month compliance period, and \$1,300 for an 18-month compliance period. No industry comment questioned the reasonableness of these unit cost estimates.

The final rule sets compliance periods of 1 year for large firms (revenues above \$20 million) and 18 months for small firms (revenues below \$20 million), except that new claims (i.e., claims not made before the publication of the final rule) must be in compliance as of the effective date. Such claims will not necessitate relabeling, however. FDA does not know the size of

the firms that will need to make label changes. RTI (Ref. 12) reports that 95 percent of the firms in the industry are small, but that the 5 percent that are large account for 80 percent of industry sales. The RTI product data base also indicates that approximately 25 percent of the sampled products were manufactured by just 5 percent of the companies. Thus, FDA has assumed that approximately one-quarter of the affected products will come from large firms and three-quarters from small firms. Consequently, the total estimated label redesign costs equal about \$3.03 million (i.e., $\$1,700 \times 0.25 \times 2,164 \text{ SKU's} + \$1,300 \times 0.75 \times 2,164 \text{ SKU's}$).

b. Administrative costs. One industry comment contended that FDA had not adequately explained the basis for its company-specific administrative costs, estimated at \$425 and \$320 respectively, for 12-month and 18-month compliance periods. These figures were derived from data presented in a 1991 RTI report on the cost of FDA's food labeling regulations (Ref. 13). They included costs associated with interpreting a regulation, determining the manner of compliance and managing the compliance method. RTI had estimated that, on average, small firms would bear administrative costs of \$850 to comply with the new food labeling rules for a 1-year compliance period, and \$650 for a 2-year compliance period. For its analysis of the proposed rule, FDA reduced this figure by fifty percent, based on the smaller administrative effort that would be needed to comply with the

proposed rule, compared to the conventional food labeling regulations evaluated by RTI in 1991. The regulations that were the subject of the 1991 RTI evaluation involved a broader range of administrative options and tasks, such as nutritional testing and product reformulation. (The \$320 estimate for the 18-month compliance period was determined by interpolating between the estimates for 12 and 24 months.) The agency has raised these costs by about 27 percent to \$540 and \$407, respectively, to account for salary inflation since 1991 (Ref. 14).

FDA had initially estimated that 500 to 850 firms manufacture dietary supplements. The recent RTI study, however, has identified 1,050 manufacturers (Ref. 12). This higher number probably overestimates the size of the industry covered by this rule, because it includes homeopathic products, which are drugs by statutory definition, and "functional foods" and sports nutrition products, which may be either conventional foods or dietary supplements depending on how they are marketed and used. For this final analysis, FDA has assumed that 1,000 companies manufacture the dietary supplement products covered by this rule. Although only a small fraction of these establishments will need to implement changes in labeling due to this rule, the agency anticipates most firms will review the final rule to assess whether their labeling will be affected.

The administrative costs of the final rule would likely be higher for those firms that will need to revise labels and lower for those firms that do not. Nevertheless, FDA assumes that, on average, all large dietary supplement manufacturers would incur costs of \$540 and all small dietary supplement manufacturers would incur costs of \$407. As noted above, RTI found that about 95 percent of the firms in this industry are small. Thus, the agency calculated administrative costs to equal about \$413,000 (i.e., 950 small firms x \$407 + 50 large firms x \$540). FDA notes that these estimates may overstate the incremental administrative costs of this final rule, because dietary supplement firms must already comply with DSHEA and this rule is meant to clarify the meaning of that act, rather than to add new requirements. Nevertheless, the agency's sensitivity analysis, presented below, doubles the above cost estimates.

c. Costs of inventory losses. The final cost component involves the value of lost inventory. FDA's preliminary analysis relied on information from an earlier nutrition labeling rule that affected the entire dietary supplement industry. That information indicated that inventory disposal costs for the entire industry would be about \$8 million for an 18-month compliance period and \$15 million for a 12-month compliance period. As explained above, FDA estimated that about 2.89 percent of the dietary supplement products will require new labels as a result of this rule (837 ÷ 29,000) and that about

three quarters of the affected products are manufactured by small firms. Thus, total inventory disposal costs are calculated at \$281,000 (i.e., \$8 million x 2.89 percent x 0.75 + \$15 million x 2.89 percent x 0.25).

d. Total direct compliance costs. As described above, FDA has assumed the direct compliance costs of this rule to be the costs associated with relabeling those dietary supplements whose labeling claims are considered disease claims under the newly defined criteria. Redesign costs are estimated at \$3.03 million, administrative costs at \$281,000, and inventory disposal costs at \$171,000. In sum, therefore, the total estimated direct compliance costs equal almost \$3.73 million.

In addition, there may be costs associated with the discussion in the final rule concerning structure/function claims made under section 201(g)(1)(C) of the act. (See response to comment 95 in section III.A.1 of this document.) The agency believes that some firms have been making structure/function claims for dietary supplements without including a disclaimer statement or notifying FDA, based on FDA's statements in a 1997 preamble (62 FR 49859 at 49860, 49863, and 49864). Because the agency has not repudiated these statements, any firm that has relied on them to make a claim for a dietary supplement will need to add the disclaimer to all applicable labels, as well as to notify FDA, according to the requirements of this section

403(r)(6) of the act and § 101.93. Because firms making such claims have not identified themselves to FDA, the agency does not have a reliable database on which to base a cost estimate of the number of firms and products that may incur costs to comply with this new provision.

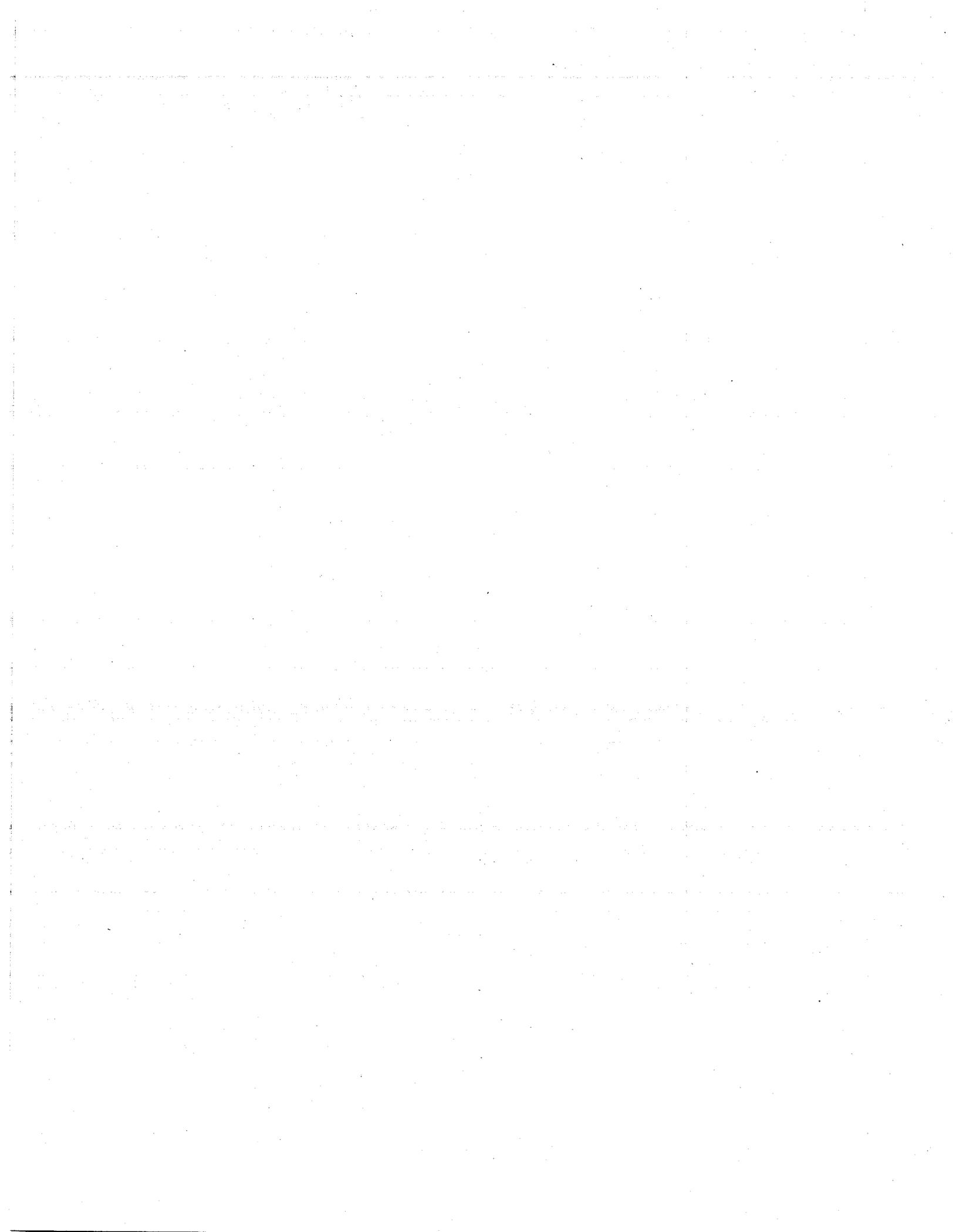
The costs to industry of the final rule are substantially different from the costs of the proposed rule, because of two important changes to the proposed requirements. First, the final rule requires more product labels to be changed, because it includes more specific parameters for acceptable structure/function claims about cholesterol. This change increases the direct compliance costs of the final rule. Second, the proposed rule required needed label modifications to be completed within 30 days after publication of the final rule, for those products without a properly submitted claim notification. Roughly 70 percent of all products with claims may have fallen into this group (1-5,200 products with notifications ÷ 17,400 products with claims). Because relabeling costs are reported to double for each halving of the compliance period, compliance costs would have been eight times greater for those products. For the final rule, all large firms will be expected to comply within 12 months, and all small firms within 18 months, regardless of whether the firm has notified FDA of the structure/function claims on its products. This change

significantly reduces the direct compliance costs of the final rule.

e. Sensitivity analysis. Due to uncertainty with respect to several factors in the agency's direct cost model, FDA has prepared a sensitivity analysis of other possible cost scenarios. First, FDA tripled the percentage of product notifications assumed to be out of compliance with the new criteria for structure/function claims. This change results in almost tripling the total direct compliance costs of the regulation, raising the estimate from about 3.73 million to about 10.35 million. Second, FDA doubled its estimate of administrative costs. This change raises the initial cost estimate to about \$4.14 million. Changing both assumptions simultaneously raises the total estimated costs to about \$11 million. Finally, under the initial scenario, if all of the needed label changes were assumed to affect only small businesses, the total cost estimate rises to about \$3.46 million. This sensitivity analysis indicates that the total direct costs of this rule would not impose a major burden on this industry even if the most uncertain cost factors are doubled or tripled from FDA's best estimates.

D. Other Industry Comments

Several comments insisted that FDA had not conducted a comprehensive cost-benefit analysis of the proposed rule, as required under Executive Order 12866. These comments stated that



FDA's economic analysis ignored both the potential savings in consumer health care expenditures that would be lost by restricting important labeling information, as well as the likely negative effect of the proposal on the growth of the dietary supplement industry. One industry comment, for example, declared that a substantive cost-benefit analysis "must identify the potential health benefits that are lost as a consequence of reduced consumer access to useful information about the health-related properties of dietary supplements and ingredients." It noted that FDA's analysis "fails to consider the public health benefits associated with ingesting dietary supplements as well as the losses to public health that could result from consumers failing to take appropriate dietary supplements due to uninformative structure/function claims." That comment also maintains that "FDA's failure to assess and consider such benefits (and costs) stands in contrast with the specific finding of DSHEA that 'appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures'." The comment also points out that FDA has performed such analyses in other rulemakings, e.g., tobacco, nutrition labeling, and ephedra regulations.

FDA disagrees. Although Executive Order 12866 directs agencies to assess the costs and benefits of economically significant rules, the quantification of these expected costs and

benefits is required only "to the extent feasible" (58 FR 51735 at 51741, October 14, 1993). As described above, FDA believes that its final rule strikes the appropriate balance with respect to health-related claims in dietary supplement labeling. The rule classifies certain claims as acceptable structure/function claims that may be made without prior FDA review. Although the provision of structure/function information to consumers may reduce health care expenditures, no health organization, industry association, or any other interested public or private group has presented information or data that would allow the agency to develop a quantifiable estimate of the health care benefits. The rule classifies other claims as disease claims that are subject to existing requirements for new drug approval or health claim authorization before a product may be marketed with the claim. FDA believes that classifying claims into a category that requires FDA review of safety and efficacy evidence, where appropriate, will similarly reduce long-term health care expenditures. Again, however, the agency has no means of quantifying the probable health outcomes of this aspect of the rule and therefore has no means of quantifying its impact on health care expenditures. Because this analysis discusses the types of benefits and costs reasonably expected, and quantifies those that can be "feasibly" quantified, the agency has, in fact, complied with the direction of Executive Order 12866.

FDA has attempted to quantify the benefits of some of its previous regulations. The agency's estimated benefits of the tobacco rule relied on a widely established risk assessment published by the American Cancer Society. Estimated benefits of the proposed ephedra rule were based on incidents identified in the agency's adverse event database. Estimated benefits of the nutrition labeling rule were derived from epidemiological studies of the consequences of dietary fat. In each case, the agency believed that it had a reasonably reliable data base upon which to base conclusions, and each risk assessment dealt with the risks of a single substance (tobacco, ephedra, and dietary fat). In contrast, this structure/function rule governs structure/function claims in the labeling for all dietary supplements. Although the agency could conceivably analyze a few of the claims covered by the rule, adequate data on the benefits and risks of most of these products are not available. Consequently, the agency believes that this rule will improve the nation's health, but concludes that it cannot feasibly quantify the effects of the rule on the nation's health expenditures.

One industry comment suggested that the regulatory system could impede firms from conducting research to substantiate structure/function claims, if DSHEA is construed so narrowly that it excludes meaningful health-related benefits. This comment noted, however, that the absence of an enforceable legal standard

for substantiation would discriminate against companies that do research to support their claims and would deter science-based companies from entering the market. Similarly, a patient organization and several pharmaceutical companies expressed concern that the rule would permit some products to escape regulation as drugs and therefore diminish incentives for the costly clinical research conducted by pharmaceutical companies and academic scientists.

As stated previously in the document, FDA is not aware of any evidence that would indicate that the establishment of criteria for distinguishing structure/function claims from disease claims will adversely affect the conduct of scientific research. In fact, FDA believes that the final rule accords with the intent of DSHEA in promoting the enhancements to consumer health expected from the broad dissemination of structure/function information, while reducing the risks to consumer health associated with the promotion of disease treatment and/or prevention uses for products whose safety and efficacy have not been demonstrated.

E. Regulatory Alternatives

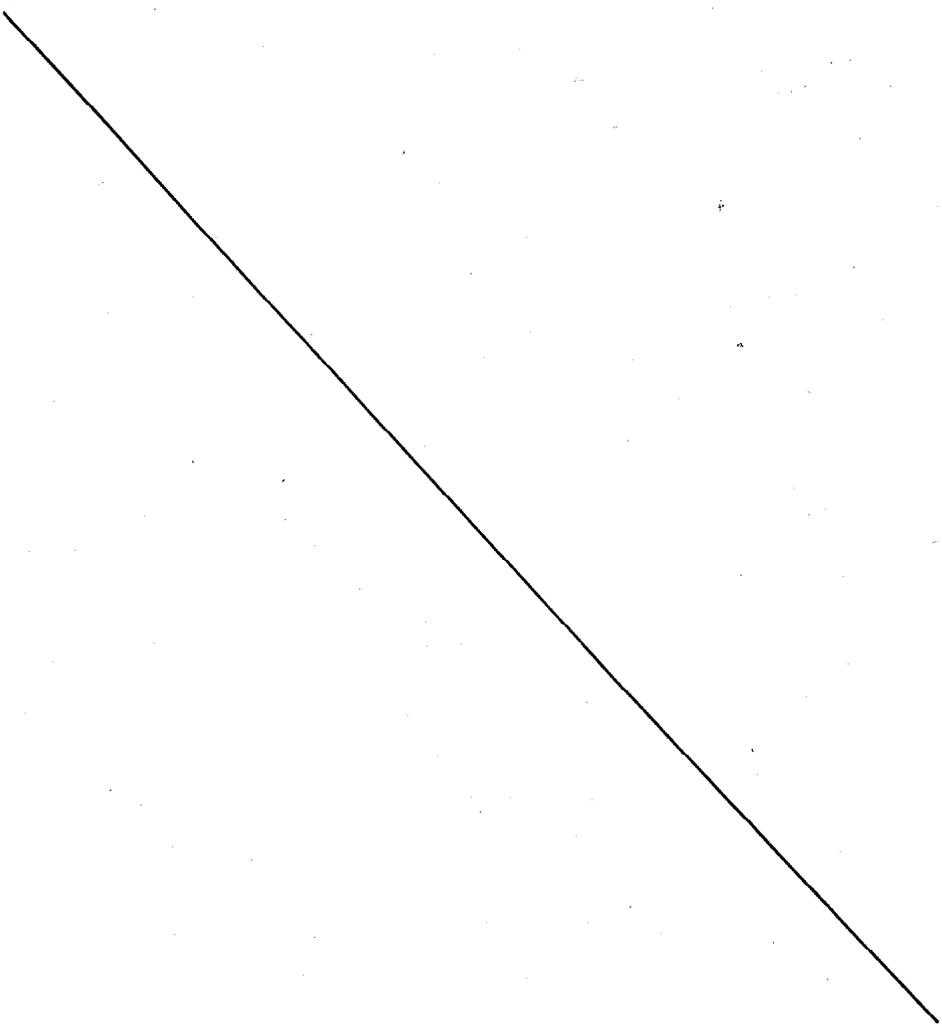
FDA has considered several major alternatives to the proposed rule as part of the rulemaking process. These include: (1) Taking no new regulatory action; (2) treating a statement about a dietary supplement as a disease claim only if the

statement included an express reference to a specific disease; and (3) treating a statement about a dietary supplement as a disease claim if the statement mentions an abnormality of the structure or function of the body, even if the abnormality was not characterized by a set of signs or symptoms recognized as the disease. These alternatives are fully discussed in the preamble to the proposed rule (63 FR 23624 at 23630), and alternative (2) is also discussed extensively in section II.E of this document. In brief, FDA finds that the public comment does not include evidence or arguments sufficient to persuade the agency to support these alternatives.

Within the broad framework of the final rule, FDA weighed other policy changes that could affect the compliance costs. One option would have set the compliance period for all firms at 6 months and another at 12 months from the publication date of the final rule. Other options would have extended the compliance period beyond 18 months for small businesses, or completely exempted small businesses from the rule. Finally, the proposed rule would have permitted firms 12 or 18 months to comply, depending on whether they were large or small firms; but only if they had submitted timely notifications of their structure/function claims to FDA and FDA had not objected to the claims. Other firms had only a 30-day compliance period.

Based on its model of food labeling costs, FDA assumes that compliance costs double for each halving of the compliance period

(Ref. 13). Thus, the first option, which set a 6-month compliance date for all firms, results in average relabeling costs twice as high as that of the 12-month compliance period. FDA decided that this additional burden was not warranted. The



option of a 12-month compliance period for small as well as large firms was rejected because of the additional burden to small firms, which may find it more difficult to effect rapid shifts in labeling procedures. The final rule provides small firms with an additional 6 months to introduce these labeling changes.

Extending the compliance date for small firms beyond 18 months was rejected, because the agency did not believe that the delayed consumer benefits would be balanced by the relatively modest additional cost saving. Exempting all small firms was not acceptable, because most firms covered by this rule are small. The final option, which was to include the compliance periods specified in the proposed rule, required label changes within 30 days for products bearing claims of which FDA had not been notified or claims to which FDA had already objected. This option was rejected because it could have increased costs per label for many small firms by a factor of eight.

F. Small Business Impacts

As stated above, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities, unless the rule is not expected to have a significant economic impact on a substantial number of small entities. With this final rule, FDA is defining the types of statements that can be made concerning

the effect of a dietary supplement on the structure or function of the body. It also establishes criteria for determining when a statement represents a claim to diagnose, cure, mitigate, treat, or prevent disease and thus is not acceptable as a structure/function claim. The regulation was prepared in response to the dietary supplement industry's request for clarification from FDA with respect to the distinction between structure/function and disease claims, and to guidance in the Commission report suggesting that FDA provide such clarification to industry.

For its analysis of the proposed rule, FDA had estimated that between 500 and 850 firms were involved in dietary supplement manufacturing. A more recent industry survey reports that 1,050 companies manufacture dietary supplements; although as explained above, some of these companies may manufacture products not covered by this rule. FDA has projected the industry size for this rule at about 1,000 firms. The Small Business Administration (SBA) has determined that dietary supplement manufacturers with fewer than 500 employees are small businesses. Because most data sources characterize firms in this industry by sales revenues rather than employment size, and because company revenues of less than \$20 million correlate reasonably well with a 500 employee threshold, FDA has received approval from the SBA to use a less-than-\$20 million sales revenue standard to

represent small dietary supplement manufacturers. Table 1 displays the reported size distribution of the dietary supplement manufacturing industry.

As described above, FDA assumes that all small manufacturers of dietary supplements will incur administrative costs of about \$407 per firm. In addition, a number of small manufacturers of dietary supplements will need to alter some product labels, at an average redesign cost of about \$1,300 per SKU, and an average inventory cost of about \$107 per SKU. FDA further analyzed the dietary supplement product data base described in the October 1999 RTI report (Ref. 11) to determine how these products may be distributed among small businesses. As noted earlier, FDA estimates that about 628 of the 837 products (75 percent) needing revised labels due to this rule are manufactured by small firms. If these 628 products were randomly distributed among the 950 small businesses, less than 0.1 percent of the small firms (1 firm) would be likely to have more than 4 of these products and only about 3 percent (30 firms) to have more than 2 of these products.

A small firm that needs to redesign labels for three products (about eight SKU's) due to the rule will incur estimated one-time direct compliance costs of about \$11,650. A small firm that needs to redesign labels for 4 products (about 10 SKU's) would incur costs of about \$14,950, or roughly 1.2 percent of average company revenue. Thus, the assumption that these products are randomly distributed among small firms indicates

that very few small businesses would be likely to incur relabeling costs that are greater than 1 percent of average small company revenue. It is possible, however, that some firms will have a disproportionate number of labels to be revised. In the RTI data base of 3,000 randomly selected products, only 3 companies (all large) have more than 24 products. Although the data base sample show a number of small companies with up to 24 products, it is very unlikely that all of these product labels would need to be changed due to this rule. If a small company needed to revise 10 products, however, its direct costs of compliance would be about \$37,000. Moreover, although FDA cannot quantify the likelihood, some small firms could lose product sales due to the necessary removal of a disease claim from a product label. Thus, FDA finds that this rule may have a significant economic impact on a substantial number of small companies.

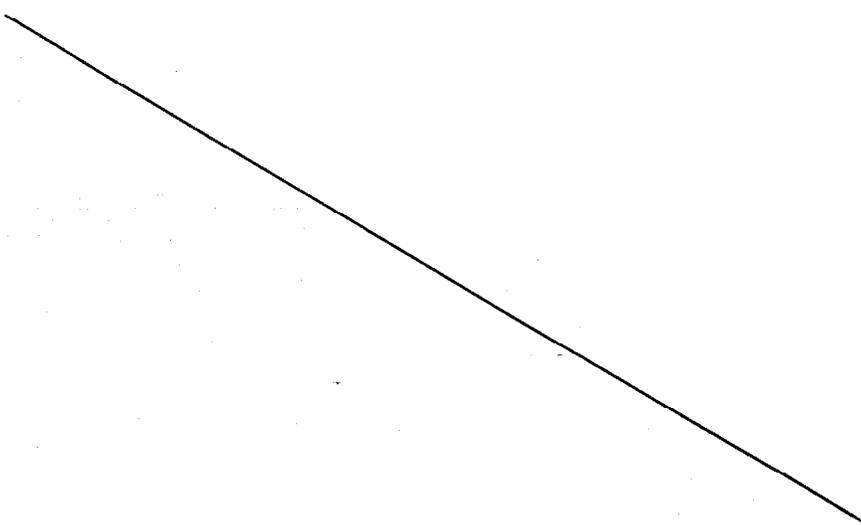


Table 1.--Estimated Number of Dietary Supplement Manufacturers and Revenues, by Size Category¹

Size Category	Number of Companies	Revenues (\$ in billions)	Percentage of Market
> \$100 million	16	3.32	55%
\$20 to \$100 million	38	1.54	25%
< \$20 million	996	1.19	20%
Total	1,050	6.05	100%

¹Research Triangle Institute, "Economic Characterization of the Dietary Supplement Industry," March 1999, pp. 5-15.

VII. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Commission on Dietary Supplement Labels, Report to the President, Congress, and the Secretary of the Department of Health and Human Services, November 1997.

2. Dorland's Illustrated Medical Dictionary, 28th ed., W. B. Saunders Co., Philadelphia, p. 478, 1994.
3. Stedman's Medical Dictionary, 26th ed., Williams & Wilkins, Baltimore, p. 492, 1995.
4. The Encyclopedia Americana, International Edition, Grolier Inc., Danbury, p. 168, 1985.
5. Black's Law Dictionary, 6th ed., West Publishing Co., St. Paul, p. 467, 1990.
6. The Merck Manual, 17th ed., Merck Research Laboratories, Whitehouse Station, NJ, p. 416, 1999.
7. Webster's Encyclopedic Unabridged Dictionary, p. 1057, 1989.
8. Economic Characterization of the Dietary Supplement Industry, prepared for DHHS/FDA/CFSAN by Research Triangle Institute, Center for Economics Research under Contract No. 223-96-2290: Task Order 3, Final Report, p. 5-2, March 1999.

9. Herb and Supplement Usage Nears 70 Percent, Natural Foods Merchandiser, www.nfm-online.com/nfm_backs/Feb_98/herbusage.html.

10. Wyngate, P., Consumers Not Supplement Brand Savvy, Natural Foods Merchandiser, www.nfm-online.com/nfm_backs/Mar_98/brandsavvy.html.

11. Dietary Supplement Sales Information, prepared for DHHS/FDA/CFSAN by Research Triangle Institute, Center for Economics Research under contract No. 223-96-2290: Task Order 4, Final Report, pp. 5-8, October 1999.

12. Research Triangle Institute, Economic Characterization of the Dietary Supplement Industry, p. 5-15.

13. Research Triangle Institute, "Compliance Costs of Food Labeling Regulations," prepared for CFSAN/FDA by RTI under Contract No. 223-87-2097, final report, pp. 5-3, 5-4, January 1991.

14. U.S. Department of Labor, Bureau of Labor Statistics, BLS.

15. Memorandum from R.J. Moore, FDA, to file, review of notifications made pursuant to 21 U.S.C. 343(r)(6).

16. Memorandum from J. Lienesch, FDA, to file, calculation of relabeling cost estimate for final rule on statements made of dietary supplements concerning the effect of the production on the structure of function of the body, December 22, 1999.

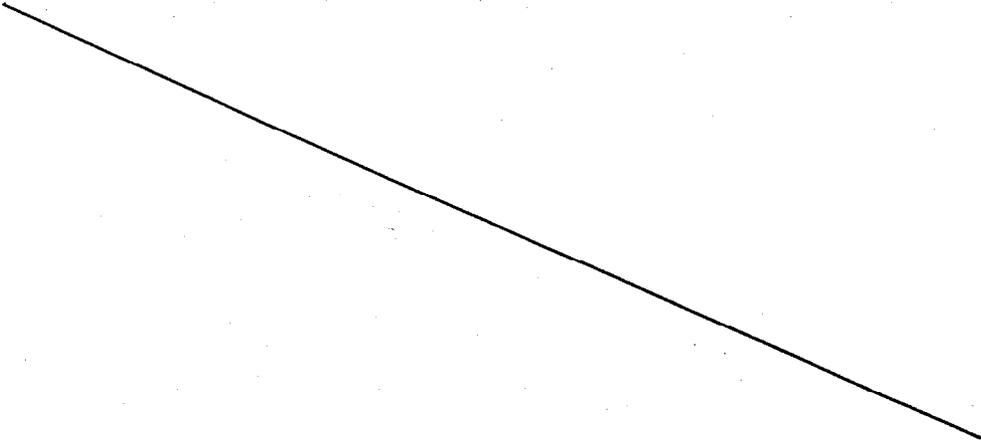
List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101--FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:



Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371.

2. Section 101.93 is amended by revising the section heading and by adding paragraphs (f) and (g) to read as follows:
§ 101.93 Certain types of statements for dietary supplements.

* * * * *

(f) Permitted structure/function statements. Dietary supplement labels or labeling may, subject to the requirements in paragraphs (a) through (e) of this section, bear statements that describe the role of a nutrient or dietary ingredient intended to affect the structure or function in humans or that characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, provided that such statements are not disease claims under paragraph (g) of this section. If the label or labeling of a product marketed as a dietary supplement bears a disease claim as defined in paragraph (g) of this section, the product will be subject to regulation as a drug unless the claim is an authorized health claim for which the product qualifies.

(g) Disease claims. (1) For purposes of 21 U.S.C. 343(r)(6), a "disease" is damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases

resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition.

(2) FDA will find that a statement about a product claims to diagnose, mitigate, treat, cure, or prevent disease (other than a classical nutrient deficiency disease) under 21 U.S.C. 343(r)(6) if it meets one or more of the criteria listed below. These criteria are not intended to classify as disease claims statements that refer to the ability of a product to maintain healthy structure or function, unless the statement implies disease prevention or treatment. In determining whether a statement is a disease claim under these criteria, FDA will consider the context in which the claim is presented. A statement claims to diagnose, mitigate, treat, cure, or prevent disease if it claims, explicitly or implicitly, that the product:

- (i) Has an effect on a specific disease or class of diseases;
- (ii) Has an effect on the characteristic signs or symptoms of a specific disease or class of diseases, using scientific or lay terminology;
- (iii) Has an effect on an abnormal condition associated with a natural state or process, if the abnormal condition is uncommon or can cause significant or permanent harm;
- (iv) Has an effect on a disease or diseases through one or more of the following factors:

(A) The name of the product;

(B) A statement about the formulation of the product, including a claim that the product contains an ingredient (other than an ingredient that is an article included in the definition of "dietary supplement" under 21 U.S.C. 321(ff)(3)) that has been regulated by FDA as a drug and is well known to consumers for its use or claimed use in preventing or treating a disease;

(C) Citation of a publication or reference, if the citation refers to a disease use, and if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease, e.g., through placement on the immediate product label or packaging, inappropriate prominence, or lack of relationship to the product's express claims;

(D) Use of the term "disease" or "diseased," except in general statements about disease prevention that do not refer explicitly or implicitly to a specific disease or class of diseases or to a specific product or ingredient; or

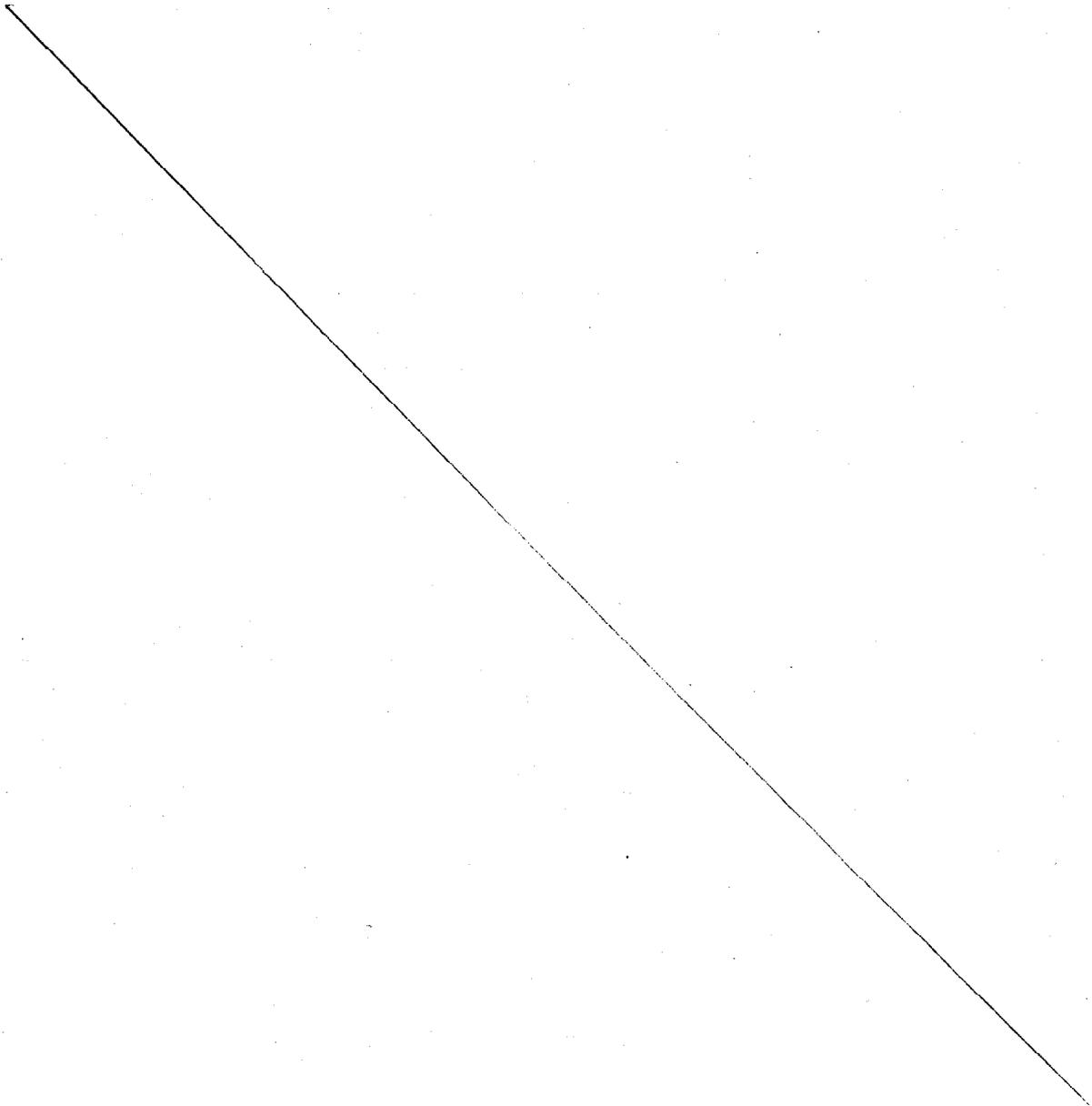
(E) Use of pictures, vignettes, symbols, or other means;

(v) Belongs to a class of products that is intended to diagnose, mitigate, treat, cure, or prevent a disease;

(vi) Is a substitute for a product that is a therapy for a disease;

(vii) Augments a particular therapy or drug action that is intended to diagnose, mitigate, treat, cure, or prevent a disease or class of diseases;

(viii) Has a role in the body's response to a disease or to a vector of disease;



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¶ (ix) Treats, prevents, or mitigates adverse events associated with a therapy for a disease, if the adverse events constitute diseases; or

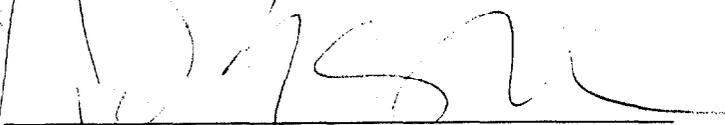
(x) Otherwise suggests an effect on a disease or diseases.

OCT 20 1999

Dated: _____



Jane E. Henney,
Commissioner of Food and Drugs



Donna E. Shalala
Secretary of Health and Human Services

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