



Council for Responsible Nutrition

1828 L Street, NW, Suite 510 • Washington, DC 20036-5114
(202) 204-7700 • fax (202) 204-7701 • www.crnusa.org

July 7, 2017

VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses” [Docket No. FDA–2015–N–2002]

The Council for Responsible Nutrition (CRN)¹ respectfully submits these comments on the Food and Drug Administration’s (FDA’s) request for comments² on its Final Rule entitled *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses”* (Final Rule).³

CRN is pleased that FDA has further delayed the effective date of the Final Rule in response to the Citizen Petition filed by the Medical Information Working Group and other groups.⁴ We agree that the Final Rule’s expansive “totality of evidence” standard raises multiple concerns. In particular, the Final Rule will have legal implications for research and product development in the dietary supplement and food industry, thereby stifling innovation and negatively impacting

¹ The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional food, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN’s Code of Ethics. Learn more about us at www.crnusa.org.

² *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses”*; *Further Delayed Effective Date; Request for Comments*, 82 Fed. Reg. 14319 (Mar. 20, 2017).

³ 82 Fed. Reg. 2193 (Jan. 9, 2017).

⁴ See February 8, 2017 petition submitted by Ropes & Gray and Sidley Austin LLP on behalf of the Medical Information Working Group, the Pharmaceutical Research and Manufacturers of America, and the Biotechnology Innovation Organization, available in Docket No. FDA–2011–P–0512 [hereinafter “Citizen Petition”].

public health. Although the comments herein focus primarily on dietary supplements, our comments apply equally to functional food and medical food, as manufacturers seeking to ensure the safety and efficacy of these products will face the same obstacles under the Final Rule.

Robust clinical investigations are essential for providing beneficial and safe dietary supplements and ensuring that dietary supplement claims are adequately substantiated. CRN also recognizes the importance of maintaining the distinction between products that are promoted to prevent, treat, cure, or mitigate disease (i.e., drugs) and which clearly require an Investigational New Drug Application (IND), and those that are intended to be marketed as dietary supplements or foods. However, FDA's Final Rule departs from past Agency practice and potentially creates uncertainty as to the circumstances under which a product such as a dietary supplement would be regulated as a drug—merely because of a clinical endpoint used in research. Thus, CRN urges FDA to affirm that clinical trial research protocols will not be part of the Agency's new "totality of the evidence" standard. FDA should maintain its historical approach to determining intended use through marketing representations and claims made in labeling.

I. The New "Totality of the Evidence" Standard Expands the Definition of "Drug" and Could Create Uncertainty as to the Regulatory Status of Dietary Supplements

In amending the Federal Food, Drug, and Cosmetic Act (FD&CA), the Dietary Supplement Health and Education Act of 1994 (DSHEA)⁵ affirmed that dietary supplements are a subcategory of food. DSHEA also excluded a dietary supplement from the statutory definition of "drug" if it is intended to affect the structure or function of the body and if it does not claim to diagnose, cure, mitigate, treat, or prevent disease.⁶ FDA regulates products based on "intended use," which historically has been determined by the manufacturer's marketing representations and labeling of a product. But the Final Rule would amend the definitions of intended use for drugs and medical devices in 21 C.F.R. §§ 201.128 and 801.4 to create a broad "totality of the evidence" standard for establishing a manufacturer's objective intent about the use of a product. As explained below, this could result in dietary supplements being categorized as investigational new drugs based on research protocols of studies conducted only to support lawful structure/function claims, and not to be used in the development or promotion of new drugs.

We agree with FDA that a dietary supplement should not bear claims that would cause the product to be an unapproved new drug under the FD&CA. However, the new "totality of the evidence" standard not only departs from past Agency practice, but also muddles FDA's enforcement regime and creates uncertainty for industry stakeholders.

⁵ Pub. L. No. 103-417, 108 Stat. 4325 (1994).

⁶ 21 U.S.C. § 321(g)(1), further noting that such product must also meet the requirements of 21 U.S.C. § 343(r).

A. *The “Totality of the Evidence” Standard Departs From Past Agency Practice and Expands the Definition of “Drug”*

Courts have consistently upheld the Agency’s determination of intended use based on manufacturers’ marketing representations and product labeling.⁷ This approach is also supported by past statements by senior Agency officials: “It is well settled that intended use is determined with reference to marketing claims.”⁸ FDA now proposes to expand the supporting evidence that makes a product subject to regulation as a drug to include the “totality of the evidence,” a phrase that has not previously been used in this context, and which encompasses far more than marketing claims.⁹

Specifically, FDA suggests that it will include research protocols of clinical investigations as part of its “totality of the evidence” determinations.¹⁰ This would represent a shift from past Agency practice. While FDA expressed in guidance that it will consider endpoints to determine whether an IND is required for a clinical investigation,¹¹ the Agency explicitly recognized that this analysis is separate from the intended use of the article, which is based on *marketing*. FDA stated:

Under DSHEA, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs *if the intended use for which it is marketed* is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Similarly, whether an IND is needed

⁷ See, e.g., *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998) (“[N]o court has ever found that a product is ‘intended for use’ or ‘intended to affect’ within the meaning of the [Act] absent manufacturer claims as to that product’s use.”) (citing *Coyne Beahm Inc. v. FDA*, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997), *aff’d* 529 U.S. 120 (2000)). See also *United States v. Undetermined Quantities of Bottles of an Article of Veterinary Drug*, 22 F.3d 235, 239 (10th Cir. 1994) (agreeing with FDA’s argument that “the labeling and marketing claims made by [Defendant] make the substance a drug,” and noting that courts have upheld similar arguments); *Nat’l Nutritional Foods Assoc. v. Matthews*, 557 F.2d 325, 333 (2d Cir. 1977) (“The vendor’s intent in *selling* the product is the key element in [the FD&CA drug definition]”) (emphasis added); *United States v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692, 698 (D. Md. 2001) (“Of primary significance in determining whether a product may be deemed a ‘drug’ is its intended use or effect as gathered from the objective evidence *disseminated* by the vendor.”) (emphasis added).

⁸ Letter from FDA Chief Counsel Daniel E. Troy to Jeffrey N. Gibbs (Oct. 17, 2002), at 3. Mr. Troy elaborates, “Also, if foreseeability were a permissible basis for finding an intended use as that term is used in Section 201(h)(3), FDA’s jurisdiction would encompass many articles having foreseeable physical effects. Yet FDA only regulates products *if they are marketed* with claims of medical or therapeutic utility.” *Id.* at 5 (emphasis added).

⁹ Citizen Petition, *supra* note 4, at 14–19.

¹⁰ See 82 Fed. Reg. 2193 at 2213 (explaining that whether a product, as used in a study, “is subject to regulation as a drug depends on whether the product is being investigated for any of the purposes described in § 1100.5(a) or (b),” and stating that to determine if a product is being investigated for one of those purposes, FDA generally *would review the protocol for the study, including the proposed methods and measures. In the Agency’s experience, the proposed methods and measures for a study can provide insight into the purposes for which a product is being investigated*”) (emphasis added).

¹¹ FDA, Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards on Investigational New Drug Applications-Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug Application (Sept. 2013) [hereinafter “IND Guidance”].

for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation.¹²

Thus, FDA acknowledged that while the protocol and endpoints for a clinical investigation may determine whether an IND is required,¹³ it is the *marketing* of an article that determines its intended use more broadly. In promulgating the Final Rule, FDA offers no explanation for why it now states that intended use may be determined by a clinical trial protocol, and we question the rationale and legal basis for this change in Agency practice.

FDA suggests that it sees no meaningful difference between its new “totality of the evidence” standard and the previous standard under which FDA relied on “any relevant source of evidence.”¹⁴ But there is a critical distinction; the “totality of the evidence” standard is more expansive, allowing FDA to consider *all* evidence, regardless of its relevance, and even if that evidence is not tied to marketing claims. As noted in the Citizen Petition, “acts of even marginal relevance can be considered as part of a larger mix of circumstances, even if the probative force of each fact is relatively weak.”¹⁵

This distinction is of critical importance to dietary supplement manufacturers, because it could allow the Agency to regard a manufacturer as intending an unapproved new use for a dietary supplement product based on the clinical endpoint of a study conducted only to provide support for lawful structure/function claims. Thus, by including research protocols in the “totality of the evidence” assessment of intended use, FDA expands the circumstances under which a product such as a dietary supplement may be considered a drug.

B. The “Totality of the Evidence” Standard Will Create Uncertainty in the Dietary Supplement Industry and Does Not Serve the Agency’s Goal of Increased Clarity

Throughout the Final Rule, FDA emphasized that the goal of the amendments was to provide “increased clarity to stakeholders, particularly regulated entities, regarding FDA’s interpretation of which regulatory framework will apply to particular products.”¹⁶ But FDA’s new scheme

¹² *Id.* at 12.

¹³ CRN has objected, and continues to object, to this Agency approach. See Council for Responsible Nutrition, *Comments Re: Docket No. FDA-2010-D-0503. Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards on Investigational New Drug Applications-Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug Application* (April 7, 2014). It is noteworthy that due to ongoing objections from CRN and other industry stakeholders, FDA has stayed certain sections of the IND Guidance citing concerns about its impact on scientific research and the need to further consider industry comments.

¹⁴ 82 Fed. Reg. 14319 at 14322 (“In light of the petitioners’ concerns about the language in the final rule, do stakeholders believe there is a distinction between considering ‘any relevant source of evidence’ and the ‘totality of the evidence’? Do stakeholders have suggestions about what wording provides the most clarity to regulated entities?”).

¹⁵ Citizen Petition, *supra* note 4, at 15.

¹⁶ 82 Fed. Reg. 2193 at 2204; see also *id.* at 2198 (“[T]he rule is intended to provide clarity for drug and device manufacturers generally regarding FDA’s interpretation and application of its existing intended use regulations.”); *id.* at 2204 (“These clarifying changes to the intended use regulations apply to drugs and devices generally, and not just to

instead *decreases* stakeholder clarity regarding the regulatory status of dietary supplements and penalizes diligent dietary supplement manufacturers seeking to support lawful structure/function claims, as required by DSHEA.

As the Supreme Court has observed, a totality standard is “not a test at all but an invitation to make an ad hoc judgment.”¹⁷ A “totality of the evidence” standard, applied on a case-by-case basis, offers no certainty for manufacturers.¹⁸ Except through experience, manufacturers will have no way to predict how much weight FDA will give to competing factors.¹⁹

The Final Rule thus creates an unprecedented challenge for manufacturers conducting studies to support lawful structure/function claims for dietary supplements; under the “totality of the evidence” standard, study research protocols might—or might not—be used against manufacturers as part of a determination of intended use. The result would likely vary in each instance, and a product could be placed in a different regulatory bucket (i.e., dietary supplement or drug) based on the endpoint of the study used to evaluate it. How a product is categorized would become an exercise in regulatory language manipulation, creating ambiguity that runs counter to the Agency’s stated goal of increased clarity.

For example, a dietary supplement may lawfully claim to support blood pressure levels already within the normal range. However, to substantiate this lawful structure/function claim, a manufacturer often must design a clinical trial to study subjects with elevated blood pressure levels—levels which may not signify a disease state (i.e., hypertension) but are at the high end of the normal range. Because FDA characterizes this endpoint as a disease endpoint, the Agency potentially could consider the study as evidence of the manufacturer’s intended use of the supplement as a drug, and therefore regulate the supplement as a drug, even if the study was only intended to support a permissible structure/function claim, and even if the product is not marketed as a drug nor intended to be marketed with disease claims.

This result is particularly problematic for dietary supplements because there are generally no validated biomarkers that could serve as surrogate endpoints for supporting claims related to “health promotion,” “wellness,” or “supporting normal structure and function.” Instead, investigators often need to assess effects such as lowering of blood pressure or serum cholesterol levels, or similar effects on other established surrogates, to adequately substantiate lawful structure/function claims. However, FDA views these effects as therapeutic effects and thus, disease endpoints. In turn, under the new standard articulated in the Final Rule, FDA could use

products made or derived from tobacco and intended for human consumption.”); *id.* at 2205 (“[T]hese amendments were intended to clarify FDA’s existing position on intended use, not to change it.”).

¹⁷ *City of Arlington v. FCC*, 133 S. Ct. 1863, 1874 (2013).

¹⁸ See Citizen Petition, *supra* note 4, at 21 (“Under a totality standard, no one will be able to know, in advance, what evidence (or even types of evidence) a prosecutor might consider sufficient to deem an actual use to be an intended use.”).

¹⁹ *Id.* at 15 (“Under a totality standard, however, FDA would be free to determine where the balance of evidence lies and to ascribe whatever probative value it chooses to circumstantial evidence, or at least could argue that another fact finder could do so.”).

the intent of the clinical investigation as part of an evaluation of the product's intended use, which may result in the product being considered an investigational new drug.

Many studies of dietary supplements are conducted by independent investigators who design studies that are appropriate to their research questions, but who have no connection with or input on a manufacturer's product development or marketing plans. Such research may involve assessing the supplements' therapeutic (disease-related) effects. Research protocols of such independent studies should not play a role in FDA's determination of a manufacturer's intended use. But the Final Rule as written could allow the Agency to include independent studies as part of its "totality of the evidence" assessment. This approach also creates a dilemma for dietary supplement manufacturers: by using robust, independent studies to substantiate a structure/function claim as required by law, a manufacturer of an otherwise lawful dietary supplement may unintentionally subject itself to an FDA determination of an intended drug use. FDA should be encouraging the dietary supplement industry to use rigorous independent research to support lawful product claims, rather than creating unnecessary confusion and obstacles to product research.

II. The "Totality of the Evidence" Standard Will Limit Research and Innovation, at the Expense of Public Health

CRN acknowledges FDA's concern that a "narrow view" of evidence of intended use could result in marketing of unapproved medical products to the detriment of public health,²⁰ and agrees with FDA that ensuring public health is the top priority. However, FDA's overly broad view of what constitutes evidence of intended use will stifle a significant body of research that seeks to promote public health.

Specifically, the Final Rule will act as a disincentive to pursuing the type of robust research needed to substantiate health-related claims, and therefore discourage investment in important research and scientific study of dietary supplements. The Final Rule may limit the willingness of manufacturers to research disease endpoints, because research protocols could later be used against manufacturers as part of a "totality of the evidence" argument in support of an intended drug use claim. Because of the difficulties in designing studies that measure health promotion for purposes of supporting a lawful structure/function claim, a large number of supplements and food components might be categorized as investigational new drugs as a result of the Final Rule.

And, by considering research protocols in determining whether studies of products that are marketed as dietary supplements are intended to be used as drugs, the Final Rule acts in opposition to the spirit of DSHEA.²¹ In enacting DSHEA, Congress noted the "benefits of dietary supplements to health promotion" and the use of supplements to "reduce long-term health care expenditures."²² DSHEA also mandates that "the Federal Government should not take any

²⁰ 82 Fed. Reg. 2193 at 2207.

²¹ Pub. L. No. 103-417, 108 Stat. 4325 (1994).

²² Pub. L. No. 103-417 § 2.

actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers.”²³

Thus, instead of advancing the public health, which is an integral part of FDA’s mission, the Final Rule threatens future research opportunities, discourages investment in health promotion studies, and impedes the development of and access to safe and lawful supplements, in contravention of Congressional intent.

III. The “Totality of the Evidence” Standard Will Impinge on First Amendment Rights by Chilling Truthful and Non-Misleading Speech

Although FDA states that the broader policy questions and First Amendment issues related to the Final Rule are being considered in a separate proceeding,²⁴ the Agency devotes several pages of the Final Rule to presenting its position on First Amendment issues.²⁵ CRN therefore believes it is important here to urge FDA to ensure it does not suppress truthful and non-misleading scientific information about health benefits when considering what constitutes evidence of intended use.

The new “totality of the evidence” standard departs from judicial precedent on the scope of the government’s ability to restrict truthful and non-misleading information. FDA acknowledges that government restrictions on commercial speech are assessed under the test applied by the Supreme Court in *Central Hudson Gas and Electric Corp. v. Public Services Commission*.²⁶ Under *Central Hudson*, government restriction of truthful speech concerning a lawful activity violates the First Amendment unless the government can establish that (1) the restriction is in furtherance of a substantial government interest; (2) directly advances that interest; and (3) is no more extensive than is necessary to serve that interest.²⁷

CRN acknowledges FDA’s substantial interest in protecting the public health by ensuring drug safety and preventing unapproved drugs from entering the marketplace. However, a “totality of the evidence” standard, under which the Agency may consider *any* statement made by a manufacturer as evidence of the manufacturer’s intended use, is not narrowly tailored to serve that interest. On the contrary, the new standard gives FDA broad authority to use truthful and non-misleading statements about clinical investigations for dietary supplements as evidence that those dietary supplements should be regulated as drugs, effectively limiting virtually *all* speech related to such clinical investigations. Several less restrictive alternatives would serve FDA’s interest in protecting the public health, including FDA’s previous approach to determining

²³ *Id.*

²⁴ 82 Fed. Reg. 2193 at 2209.

²⁵ *Id.* at 2208–11.

²⁶ 447 U.S. 557 (1980); *see* 82 Fed. Reg. 2193 at 2211 (“The Supreme Court . . . confirmed that where, as here, the speech in question is commercial, the Court applies the ‘commercial speech inquiry’ as outlined in *Central Hudson*.”).

²⁷ *Central Hudson*, 447 U.S. at 564; *see also* 82 Fed. Reg. 2193 at 2208–09.

intended use by reference to marketing claims. In fact, the Agency is already engaged in ongoing compliance and enforcement actions against companies that make disease claims, based solely on claims made in marketing.²⁸ We see no reason why FDA should expand its evidentiary basis when existing law provides the Agency with ample enforcement authority.

Notably, in FDA's recent memorandum on First Amendment considerations relating to communication of scientific information,²⁹ the Agency reflected not only this historic approach, but also court decisions focused on *promotional* speech as evidence of intended use. For example, the Agency states, "it has long been FDA policy not to consider a firm's presentation of truthful and non-misleading scientific information about unapproved uses at medical or scientific conferences to be evidence of intended use when the presentation is made in non-promotional settings and not accompanied by promotional materials."³⁰ While CRN recognizes that this statement is limited to discussions in such conferences of FDA-approved medical products and not dietary supplements, it reflects the Agency's longstanding precedent of regarding speech to be evidence of intended use only where it is promotional. Likewise, FDA's discussion of court decisions relating to speech as evidence of intended use primarily addressed promotional speech, not communications such as clinical trial protocols.³¹

Moreover, by applying the "totality of the evidence" standard to the intended use determination, FDA would discourage manufacturers from conducting studies to support lawful structure/function claims, and from sharing information regarding those studies; manufacturers may hesitate to engage in scientific research and discourse for fear that FDA will use the research protocols as evidence of intent for the product to be marketed as a drug, not as a dietary supplement.³² Such a regulatory scheme risks chilling speech that could otherwise provide a public health benefit.

IV. Conclusion

For the reasons set forth above, CRN respectfully urges FDA to clarify that research protocols will *not* be considered as part of the Agency's new "totality of the evidence" approach to determining intended use. FDA should not depart from its historical approach to determining

²⁸ If necessary, FDA also has authority to take further action, including criminal prosecutions, product seizures, and injunctions. See, e.g., FDA News Release, *Colorado Unapproved Drug and Dietary Supplement Makers Ordered to Cease Operations for Federal Violations* (Mar. 14, 2017), available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm546620.htm> (announcing federal enforcement action against a dietary supplement manufacturer for marketing with drug claims).

²⁹ FDA Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, Docket No. FDA-2016-N-1149 (Jan. 2017).

³⁰ *Id.* at 21.

³¹ E.g., *id.* at 22 ("[T]he Second Circuit later confirmed that *Caronia* left open the government's ability to prove misbranding on a theory that *promotional speech* provides evidence that a drug is intended for a use that is not included on the drug's FDA-approved label.") (emphasis added).

³² See Citizen Petition, *supra* note 4, at 20-21.

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intended use through marketing representations and claims made in labeling, which is grounded firmly in past agency practice and supported by legal precedent.

Again, thank you for the opportunity to submit these comments.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Rend Al-Mondhiry". The signature is written in a cursive style with a long horizontal stroke at the end.

Rend Al-Mondhiry
Associate General Counsel
Council for Responsible Nutrition