Council for Responsible Nutrition
1828 L Street, NW, Suite 810 • Washington, DC 20036-5114
(202) 204-7700 • fax (202) 204-7701 • www.crnusa.org

February 5, 2018

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Review of Existing General Regulatory and Information Collection Requirements of the Food and Drug Administration. Docket No. FDA-2017-N-5093. 82 Fed. Reg. 42506.

The Council for Responsible Nutrition (CRN) appreciates the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) to provide input on the review of existing regulatory and information collection requirements of the agency. CRN is the leading trade association representing dietary supplement and functional food manufacturers, marketers, and ingredient suppliers.[1]

In response to the agency's request, we have identified several FDA regulations and guidance documents that we recommend that the agency consider modifying or rescinding. CRN believes that these regulations and guidance documents are burdensome, impose considerable costs on the industry, and/or contain unnecessary information collection requirements, while not directly advancing FDA and the industry's shared goals of ensuring the manufacture and sale of safe and high-quality dietary supplements with truthful, non-misleading, and scientifically-accurate labeling.[2]

[1] The Council for Responsible Nutrition (CRN), founded in 1973, is a Washington, D.C.-based trade association representing 150+ dietary supplement and functional food manufacturers, ingredient suppliers, and companies providing services to those manufacturers and suppliers. In addition to complying with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety, our manufacturer and supplier members 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] CRN Code of Ethics (Dec. 2014), http://www.crnusa.org/about-crn/code-ethics (six ethical principles that all CRN members pledge to uphold); Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. 103-417 (requires FDA to regulate the safety, quality, and labeling of dietary ingredients and dietary supplements).

Our comments proceed in five parts, each of which represents an area that CRN believes could benefit from reconsideration by FDA, specifically, regulations or guidance related to: (I) Dietary Supplement Current Good Manufacturing Practices (cGMP); (II) Food and Dietary Supplement Labeling; (III) Food and Dietary Supplement Research; (IV) New Dietary Ingredient Notifications; and (V) the Food Safety Modernization Act (FSMA). The specific regulations are detailed by category.

I. Dietary Supplement Current Good Manufacturing Practices

CRN recommends that FDA consider modifying the following requirements in 21 C.F.R. 111: §§ 111.70, 111.75, 111.210, and 111.605, which are related to (A) Establishment of Specifications for the Dietary Supplement; (B) Documentation of the Basis for Why Meeting In-Process Specifications Will Ensure that Specifications for the Dietary Supplement are Met; (C) Establishment of Prospective Corrective Action Plans; and (D) Electronic Recordkeeping Requirements. The basis for each of these requests is below.

A. Establishment of Specifications for the Dietary Supplement

Name of Regulation	21 C.F.R. 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. §§ 111.70(b), 111.70(c), 111.70(e), 111.3, 111.30, 111.75(c), 111.80(b), 111.95(b), 111.105(c), and 111.310
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0606

- Brief Description of Concern: 21 C.F.R. § 111.70(e) requires the establishment of five types of specifications for every finished dietary supplement. In pertinent part, 21 C.F.R. § 111.70(e) states the following: "[f]or each dietary supplement that you manufacture you must establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for the limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of dietary supplement to ensure the quality of the dietary supplement."[3]

  This requirement does not provide manufacturers with the flexibility to determine which specifications are necessary to ensure the quality of the dietary supplement. Rather, it mandates the manufacturer to establish all five types of specifications regardless of whether or not all specifications are appropriate for the finished dietary supplement. Conforming to this requirement, as written, places unnecessary burden on the manufacturer without improving the safety and quality of dietary supplements.

[3] 21 C.F.R. § 111.70(e).

The purity specification is an example of a specification that may not always be appropriate for every dietary supplement. In the preamble of the final rule for dietary supplement current good manufacturing practice (cGMP), FDA states the following: "The 'purity' of a dietary supplement refers to that portion or percentage of a dietary supplement that represents the intended product. For example, amino acids generally can exist in two forms (i.e., dextro (D-, or right) and levo (L-, or left) forms) called enantiomers. Enantiomers have the same chemical formula and the same chemical structure, but differ in their three-dimensional orientation. If you manufacture a dietary supplement to provide the amino acid L-arginine, and you determine that 90 percent of the manufactured product is L-arginine and 10 percent of the manufactured product is D-arginine, you could describe your L-arginine product as '90 percent pure.' As another example, if you manufacture a mixture of triglycerides that provides polyunsaturated fatty acids in the diet, the manufactured triglycerides may contain small amounts of free fatty acids and sterols. The free fatty acids and sterols could derive, for example, from the source of the triglycerides or could be byproducts of the manufacturing process. If you determine that 95 percent of the manufactured product is the mixture of the triglycerides that provides the polyunsaturated fatty acids, and 5 percent of the product is free fatty acids and sterols, you could describe the purity of your product as '95 percent pure.'"[4]

Based on the above examples, a purity specification may not be applicable in cases where different enantiomers of a dietary ingredient or mixtures of related substances do not exist in a dietary supplement. In such cases, a specification for "purity" should not be required for the dietary supplement because it would not be practical or possible to test for the presence or absence of a component that does not exist. For example, a purity specification should not be necessary for a botanical extract supplement, because variations in "purity" (as described in the cGMP preamble) do not typically exist for botanical extracts. In general, botanical extracts are complex mixtures comprising a number of constituents, and one or more of the constituents can serve as "marker" for analytical purposes. However, the entire botanical extract is regarded as the intended product (the bioactive substance) and the purity of a botanical extract would always be regarded as 100%. In cases like this, the establishment and confirmation of specifications for identity, strength, composition and limits on likely contaminants would sufficiently ensure the quality of the dietary supplement.

Further, modifying 21 C.F.R. § 111.70 (b), (c) and (e) to allow the manufacture to determine which specifications are necessary to ensure the quality of the dietary supplement is consistent with the overall goal of 21 C.F.R. § 111.70.

- Available Data on Cost or Economic Impact: According to an economic impact analysis conducted by FDA, the cGMP regulatory requirements for dietary supplements impose considerable costs on establishments that manufacture, package, label, or hold dietary supplements.[5] FDA estimates that the annual costs on establishments would be $104 million

[4] Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements, 72 Fed. Reg. 34751 at 34803 (June 25, 2007).

[5] *Id* at 34934.

to $322 million, with the largest share attributed to satisfying the testing and recordkeeping requirements. Like FDA, we are concerned that the "costs per establishment are proportionally higher for very small than for large establishments," and agree that the "most striking result is that annual costs are highest for small establishments."[6] Overly broad directives, like those in 21 C.F.R. § 111.70, are unnecessary contributors to the burdensome compliance costs impacting these establishments.

Proposed Solution: CRN recommends that 21 C.F.R. § 111.70(b), (c) and (e) be modified as follows (new text appears in "red"). To maintain consistency throughout 21 C.F.R. 111, the regulation should be further amended to clarify that when it refers to specifications for the dietary supplement, it is referring to those specifications that are established, as appropriate, for the dietary supplement to ensure its quality. Appendix A contains suggested changes in §§111.3, 111.30, 111.75(c), 111.80(b), 111.95(b), 111.105(c), and 111.310 in addition to the suggested changes in §111.70 shown below.

§ 111.70 (b) - *For each component that you use in the manufacture of a dietary supplement, you must establish component specifications as follows: (1) You must establish an identity specification; (2) You must establish component specifications that are necessary to help ensure that established specifications for the purity, strength and composition of dietary supplements manufactured using the components are met; and (3) You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement that are necessary to help ensure the quality of the dietary supplement.*

§ 111.70 (c) - *For the in-process production: (1) You must establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that established specifications are met for the identity, purity, strength, and composition of the dietary supplement~~s~~ and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement; (2) You must provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that established specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement;*

111.70(e) - *For each dietary supplement that you manufacture you must establish appropriate product specifications, as necessary, for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for the limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of dietary supplement to ensure the quality of the dietary supplement.*

---

[6] *Id.* at 34938. While very small establishments (under 20 employees) face annual costs of $46,000 and small establishments (20 to 499 establishments would face annual costs of $184,000, large establishments (500+ employees) would face $69,000 in annual costs.

B. Documentation of the Basis for Why Meeting In-Process Specifications Will Help Ensure Specifications for the Dietary Supplement are Met

Name of Regulation	21 C.F.R. 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 111.70(c)(2) and 21 C.F.R. § 111.75(c)-(d)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0606

- Brief Description of Concern: Under 21 C.F.R. § 111.70(c)(2),[7] manufacturers must document the basis for why meeting in-process specifications will help ensure that specifications are met for the dietary supplement. This requirement is redundant under certain circumstances, for example, when the manufacturer chooses to conduct tests or examinations to verify that specifications are met for every batch of a finished dietary supplement, as allowable under 21 C.F.R. § 111.75(c).[8]

  We agree that documentation of the basis for why meeting in-process specifications will help ensure that specifications for the dietary supplement are met may be warranted when reduced testing plans are implemented for finished dietary supplements, or when certain specifications are exempt from verification under 21 C.F.R. § 111.75(d).[9] However, the documentation required in 21 C.F.R. § 111.70(c)(2) is unnecessary and redundant for specifications that a manufacturer chooses to verify by testing every batch of a finished product.

[7] 21 C.F.R. § 111.70(c)(2) states the following: "(2) You must provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement."

[8] 21 C.F.R. § 111.75(c) states the following: "(c) For a subset of finished dietary supplement batches that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement."

[9] 21 C.F.R. § 111.75(d) states the following: "(d)(1) You may exempt one or more product specifications from verification requirements in paragraph (c)(1) of this section if you determine and document that the specifications you select under paragraph (c)(1) of this section for determination of compliance with specifications are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage. In such a case, you must document why, for example, any component and in-process testing, examination, or monitoring, and any other information, will ensure that such exempted product specification is met without verification through periodic testing of the finished batch; and (2) Your quality control personnel must review and approve the documentation that you provide under paragraph (d)(1) of this section."

- Available Data on Cost or Economic Impact: see response to Section I.A.

- Proposed Solution: Revise 21 C.F.R. § 111.70(c)(2) to specify that when a manufacturer chooses to verify a specification for every batch of the finished dietary supplement, the manufacturer may exempt that specification from the documentation requirements in 21 C.F.R. § 111.70(c)(2).

C. Establishment of Prospective Corrective Action Plans

Name of Regulation	21 C.F.R. 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 111.75(i) and 21 C.F.R. § 111.210(h)(5)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0606

- Brief Description of Concern: The aforementioned FDA regulation requires firms to create prospective corrective action plans and for such plans to be included in the master manufacturing record (MMR) of the manufacturer, packager, labeler, or holder or a dietary supplement. In pertinent part, the regulation states that "[y]ou must establish corrective action plans for use when an established specification is not met"[10] and that the "master manufacturing record must include . . . written instructions, including . . . [c]orrective action plans for use when a specification is not met."[11]

  It is not feasible to predict the full range of scenarios and circumstances that may lead to a product specification failure and, even when a scenario can be contemplated, there are often a number of different variables that can impact whether a potential corrective action is appropriate. The requirements, as written, direct firms to develop prospective corrective action plans that, in practice, may not be useful for the compliance concerns that are actually faced by the firm. With this in mind, CRN recommends that FDA consider modifying the rule to also permit the development of corrective action plans in conjunction with material reviews and disposition decisions after a specification failure, so that the regulation does not focus on the time the plan was developed. The key to product safety and integrity is the implementation of corrective actions, not the timing of when they are developed.

- Available Data on Cost or Economic Impact: see response to Section I.A.

[10] 21 C.F.R. § 111.75(i).

[11] 21 C.F.R. § 111.210(h)(5).

- Proposed Solution: Revise 21 C.F.R. § 111.75(i) and 21 C.F.R. § 111.210(h)(5) to remove the requirements to establish prospective corrective action plans and to include such plans in the MMR. Instead, FDA should require the development of corrective action plans, as needed, so that they can be developed both before and after it is determined that a specification is not met.

D. Electronic Recordkeeping Requirements

Name of Regulation	21 C.F.R. 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 111.605(c) and 21 C.F.R. pt. 11
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0606

- Brief Description of Concern: The dietary supplement cGMPs require that electronic records be maintained in accordance with FDA's standards for electronic records, under 21 C.F.R. pt. 11.[12]

  Part 11, however, imposes requirements that are particularly onerous on small establishments, including the "validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."[13] Given that FDA does not impose compliance with part 11 on manufacturers of conventional food products, we request that FDA consider eliminating this requirement for dietary supplements so that the record keeping requirements for both conventional food (see 21 C.F.R. § 117.305(g)) and dietary supplement products are consistent.

- Available Data on Cost or Economic Impact: see response to Section I.A.

- Proposed Solution: Strike 21 C.F.R. § 111.605(c), and insert "Records that are established or maintained to satisfy the requirements of this part and that meet the definition of electronic records in § 11.3(b)(6) of this chapter are exempt from the requirements of part 11 of this chapter."

II. Food and Dietary Supplement Labeling

CRN recommends that FDA consider modifying or rescinding the following regulations: 21 C.F.R. §§ 101.9, 101.14, 101.36, and 101.54, which cover: (A) Labeling of Vitamins and Minerals; (B) Labeling of Vitamin K; (C) Limitations on Nutrient Content Claims; (D) Labeling of Probiotic Quantity; (E) Labeling of Enzyme Quantity; (F) Calculation of Protein Content in

[12] 21 C.F.R. § 111.605(c) states the following: "All electronic records must comply with part 11 of this chapter."

[13] 21 C.F.R. § 11.10.

Food and Dietary Supplements; (G) the Definition of Dietary Fiber; and (H) Fat Disclosures for Nutrient Content Claims Made About the Level of Dietary Fiber. CRN also recommends that FDA update its *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims-Final* (I). The basis for each of these requests is below.

A. Labeling of Vitamins and Minerals

Name of Regulation	Nutrition Labeling of Food
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 101.9(c)(8)(v)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0813

- Brief Description of Concern: Current vitamin nomenclature regulations in 21 C.F.R § 101.9 indicate that vitamin nomenclature used in the Ingredient Declaration lines differs from the Nutrition Facts panel. Vitamins in the Ingredient Declaration must be listed by their common and usual name (e.g., ascorbic acid), whereas the letter names are more commonly permitted in the Nutrition Facts panel (e.g., Vitamin C). We support the citizen petition submitted by DSM Nutritional Products, LLC which requests that FDA amend the regulation to allow the use of simple vitamin letter names on both the Nutrition and Supplement Facts label and Ingredient Declaration lines.[14] The simplified vitamin naming conventions would apply to vitamins when added for nutritive value only.

  As DSM's citizen petition notes, the mixed naming convention for vitamins is confusing to consumers, many of whom do not understand the chemical name of a vitamin or mineral, and may not perceive these names as "healthy."[15] CRN agrees that consistently calling the ingredient by the name most commonly understood by consumers (e.g., Vitamin C, as opposed to ascorbic acid) would help reduce consumer confusion and would help consumers more easily recognize vitamin-fortified foods, thereby contributing to the nutrient density of their diets. As FDA has long recognized, the "achievement and maintenance of a desirable level of nutritional quality in the nation's food supply is an important public health objective."[16]

  Allowing the simple vitamin letter names to be displayed on both the Nutrition and Supplement Facts label and Ingredient Declaration lines will simplify the overall label and reduce the amount of space needed on pack. If manufacturers choose to use the vitamin letter name only,

[14] Citizen Petition from DSM Nutritional Products, LLC [FDA-2017-P-6211] (Oct. 19, 2017), https://www.regulations.gov/document?D=FDA-2017-P-6211-0001.

[15] *Id*. at 4-5 (Citing a 2016 survey, conducted by the International Food and Information Council (IFIC), in which consumers were asked to rate the "healthfulness" of a list of ingredients. According to the survey, 42 percent of consumers were unaware of the term "ascorbic acid," and while 83 percent rated Vitamin C as healthy, only 21 percent rated ascorbic acid as healthy.").

[16] 21 C.F.R. § 104.20 (FDA's Statement of Purpose related to the nutritional quality guidelines for food).

they would be obligated to provide the form of the vitamin upon request by a QR code or another acceptable format.

- Available Data on Cost or Economic Impact: n/a

- Proposed Solution: Modify 21 C.F.R. § 101.9(c)(8)(v) to allow for the use of simple vitamin letter names on both the Nutrition/Supplement Facts label and Ingredient Declaration line.

B. Labeling of Vitamin K

Name of Regulation	Nutrition Labeling of Food
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 101.9(c)(8)(iv)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0813

- Brief Description of Concern: The final rule on the Revision of the Nutrition and Supplement Facts Labels established in § 101.9(c)(8)(iv), a Reference Daily Intake (RDI) for vitamin K of 120 mcg based on the Adequate Intake (AI) that pertains only to phylloquinone, or vitamin K_1. However, CRN contends that the contribution of menaquinone (vitamin K_2) to the nutritional requirements for vitamin K, its role in human health, and its availability in commonly consumed foods support an expansion of the definition of vitamin K for nutrition and supplement labeling purposes to include vitamin K_2 as well. This expansion would be in line with other regulatory bodies, such as the European Food Safety Authority (EFSA), which recognizes vitamin K_2 as a source of vitamin K[17], as well as Health Canada, which permits the statement "Helps to prevent vitamin K deficiency" for both vitamin K_1 and vitamin K_2 in multivitamin/mineral supplements.[18] CRN previously raised concerns about the restricted definition of vitamin K in comments to the proposed rule on the Revision of Nutrition and Supplement Facts Labels, and outlined the evidence supporting the position that the definition of vitamin K should include vitamin K_2.[19]

- Available Data on Cost or Economic Impact: n/a

- Proposed Solution: Expand the definition of vitamin K for nutrition and supplement labeling purposes to include menaquinone (vitamin K_2).

---

[17] Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission on the safety of 'Vitamin K2'. The EFSA Journal (2008) 822, 1-32.

[18] Multi-vitamin/mineral supplement monograph. Health Canada (2007).

[19] CRN Comments to Food Labeling: Revision of the Nutrition and Supplement Facts Label [FDA-2012-N-1210] (Aug. 1, 2014), http://www.crnusa.org/sites/default/files/pdfs/comments-pdfs/CRN_Comments_FDA_ProposedRule-RevisionNutritionSupplementFactsLabels080114.pdf.

C. Limitations on Nutrient Content Claims

Name of Regulation	Nutrient Content Claims -- General Principles
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. §§ 101.54(a) and 101.54(c)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0813

- Brief Description of Concern: 21 C.F.R. § 101.54(c) imposes limits on "good source" nutrient content claims.[20] Label statements using "Good source," "contains," or "provides" are considered to be nutrient content claims and are limited to those nutrients that have an established Reference Daily Intake (RDI) or Daily Reference Value (DRV).[21]

  CRN believes that label statements using the words "contains" or "provides" should not be limited to ingredients with established RDIs or DRVs, because advances in nutrition science have shown that there are several bioactive ingredients without established RDIs or DRVs that have been demonstrated to be beneficial to human health. CRN believes, for example, that consumers would benefit from knowing that products "contain" or "provide" bioactives, including: lutein, a macular pigment that supports eye health; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), omega-3 fatty acids that support cardiovascular health; and polyphenols, which support the body's response to oxidative stress and inflammation.

  Additionally, because the government takes a considerable amount of time to update RDIs and DRVs, the current policies further restrict manufacturers' ability to communicate important and relevant information to consumers.

- Available Data on Cost or Economic Impact: n/a

[20] 21 C.F.R. § 101.54(c) states the following: *"Good Source" claims.* (1) The terms "good source," "contains," or "provides" may be used on the label and in the labeling of foods, except meal products as defined in 101.13(l) and main dish products as defined in 101.13(m), provided that the food contains 10 to 19 percent of the RDI or the DRV per reference amount customarily consumed.

[21] 21 C.F.R. § 101.54(a) states the following: (a) General requirements. Except as provided in paragraph (e) of this section, a claim about the level of a nutrient in a food in relation to the Reference Daily Intake (RDI) established for that nutrient in §101.9(c)(8)(iv) or Daily Reference Value (DRV) established for that nutrient in §101.9(c)(9), (excluding total carbohydrates) may only be made on the label or in labeling of the food if:

(1) The claim uses one of the terms defined in this section in accordance with the definition for that term;

(2) The claim is made in accordance with the general requirements for nutrient content claims in §101.13; and

(3) The food for which the claim is made is labeled in accordance with §101.9, §101.10, or §101.36, as applicable.

- Proposed Solution: Revise 21 C.F.R. §§ 101.54(a) and 101.54(c) to remove the requirement for label statements using the words "contains" or "provides" to be limited to ingredients with established RDIs or DRVs. Such label statements should be permitted for bioactives that have been shown in the scientific literature, or recognized by the National Institutes of Health or other authoritative bodies, to be beneficial to human health, regardless of whether they have established RDIs or DRVs.

D. Labeling of Probiotic Quantity

Name of Regulation	Nutrition Labeling of Dietary Supplements
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. §§ 101.36(b) and 101.36(c)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0813

- Brief Description of Concern: The current requirements for labeling the quantitative amount of "other dietary ingredients" are not appropriate for some dietary ingredients, including probiotics, and should be updated. 21 C.F.R. § 101.36 requires that the quantitative amount of probiotic ingredients be declared by weight:

    - 21 C.F.R. § 101.36(b)(3)(ii) requires that the quantitative amount of "other dietary ingredients," which includes probiotics, be declared in weight per serving.
    - 21 C.F.R. § 101.36(c)(2) indicates that "other dietary ingredients" contained in the proprietary blend be declared in descending order of predominance by weight.
    - 21 C.F.R. § 101.36(c)(3) requires that the quantitative amount by weight specified for the proprietary blend shall be the total weight of all other dietary ingredients contained in the proprietary blend.

  Probiotics are live microorganisms and declaration of weight does not indicate the viability of probiotics in the product throughout shelf life. The quantity in Colony Forming Units (CFUs) represents the amount of viable microorganisms in the product and is the scientifically accepted unit of measure for probiotics. Providing science-based, accurate labeling information will help consumers and healthcare professionals make informed choices. Accordingly, CRN and the International Probiotics Association's (IPA's) *Best Practices Guidelines for Probiotics* recommends that the quantitative amount of probiotics in a product be expressed in CFUs.[22] Further, CRN has previously supported a citizen petition submitted by IPA requesting that

[22] Best Practices Guidelines for Probiotics, CRN, http://www.crnusa.org/sites/default/files/pdfs/CRN-IPA-Best-Practices-Guidelines-for-Probiotics.pdf.

FDA amend 21 CFR §101.36 to require the quantitative amount of probiotic ingredients in dietary supplements to be declared in CFUs instead of by weight on product labels.[23]

- Available Data on Cost or Economic Impact: n/a

- Proposed Solution: Amend 21 C.F.R. § 101.36(b)(3)(ii) to require that the quantitative amount of probiotic dietary ingredients be declared in CFUs instead of by weight. For proprietary blends, amend 21 CFR § 101.36(c)(2) and 21 CFR § 101.36(c)(3) to require the quantity of a proprietary blend consisting of probiotics to be declared in CFUs, and to require the individual probiotic dietary ingredients in the probiotic proprietary blend to be declared in descending order of predominance by CFUs.

E. Labeling of Enzyme Quantity

Name of Regulation	Nutrition Labeling of Dietary Supplements
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 101.36(b)(3)(ii)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0813

- Brief Description of Concern: 21 C.F.R. § 101.36(b)(3)(ii) requires that the quantitative amount of "other dietary ingredients," which includes enzymes, be declared in weight per serving.
- As discussed in Section II.C., the current requirements for labeling the quantitative amount of "other dietary ingredients" are not appropriate for some dietary ingredients, including enzymes, and should be updated. As written, the regulation requires ingredients to be labeled with metric measures, which are not meaningful units of measure for enzymes. Enzymes are proteins that catalyze specific chemical reactions, and it is this catalytic activity (and not a metric unit) for which enzymes are used as dietary supplements. The scientifically-accepted method to measure enzyme activity is through enzymatic activity assays (which measure the ability of a given enzyme to catalyze a specific reaction under specific conditions, including time, temperature, and pH), rather than through metric units. In particular, the CRN and Enzyme Technical Association's *Best Practices Guide for Enzyme Dietary Supplement Products*[24] recommends that manufacturers provide a measure of potency (enzyme activity units) in addition to mass (mg) for individual enzymes.

- Available Data on Cost or Economic Impact: n/a

[23] CRN Comments on Citizen Petition from International Probiotics Association [FDA-2016-P-3968] (March 7, 2017), https://www.crnusa.org/sites/default/files/pdfs/comments-pdfs/Citizen%20Petition%20from%20IPA%20Support%20Letter_CRN.pdf.

[24] Best Practices Guide: Enzyme Dietary Supplement Products, CRN, http://www.crnusa.org/sites/default/files/pdfs/CRN-ETA-BPG-Enzymes2013.pdf.

- Proposed Solution: Amend 21 C.F.R. § 101.36(b)(3)(ii) to require that the amount of enzymes in a dietary supplement be labeled with both metric units and activity units for individual enzymes.

F. Calculation of Protein Content in Food and Dietary Supplements

Name of Regulation	Nutrition Labeling of Food; Nutrition Labeling of Dietary Supplements
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 101.9(c)(7) and 21 C.F.R. § 101.36(b)(2)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0813

- Brief Description of Concern: Under 21 C.F.R. § 101.9(c)(7), "[p]rotein content may be calculated on the basis of the factor 6.25 times the nitrogen content of the food as determined by the appropriate method of analysis as given in the 'Official Methods of Analysis of the AOAC International.'" The regulation should be updated to provide clarity with respect to how protein quantity should be calculated and to indicate that non-protein nitrogen-containing substances should not be counted toward total protein content on product labels.

  It is important to provide science-based, accurate labeling information to help consumers and healthcare professionals make informed choices. While amino acids are the building blocks of protein, the addition of individual amino acids to a protein product may not stimulate protein synthesis in the body.[25] As discussed in CRN's *Guidelines for the Labeling of Protein in Dietary Supplements and Functional Foods*,[26] non-amino acid substances, such as taurine or creatine, are not components of proteins, and the nitrogen contained in these compounds does not play a direct role in protein nutrition. Under the current regulation, however, the nitrogen in such substances could be counted toward total protein content.

- Available Data on Cost or Economic Impact: n/a

- Proposed Solution: Revise 21 C.F.R. § 101.9(c)(7) and 21 CFR § 101.36(b)(2) such that the quantity of protein in a product is calculated to include only proteins that meet the following definition: "a chain of amino acids connected by peptide bonds." Further, non-protein nitrogen-containing (NPN) substances should not be counted toward total protein content on

[25] While high-quality protein provides all of the amino acids required by the body (in the proper ratios) to allow for optimal rates of protein synthesis for physiological functions, individual amino acids, if added in an unbalanced manner (i.e., distorting the amino acid ratio provided by high quality protein) may not further increase protein synthesis.

[26] Guidelines for Labeling of Protein in Dietary Supplements and Functional Foods, CRN, http://www.crnusa.org/self-regulation/voluntary-guidelines-best-practices/crn-guidelines-labeling-protein-dietary.

product labels. NPN substances should be accounted for and subtracted from the total nitrogen content when protein is measured by nitrogen content.

G. Definition of "Dietary Fiber"

Name of Regulation	Nutrition Labeling of Food
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 101.9(c)(6)(i)
Approved Information Collection and OMB Control Number	OMB Control No. 0910-0813

- Brief Description of Concern: The definition of dietary fiber, as established in the 2016 final rule on the Revision of the Nutrition and Supplement Facts Labels[27], is overly restrictive. Under 21 C.F.R. § 101.9(c)(6)(i), fiber ingredients that are "intrinsic and intact in plants" automatically meet the definition of "dietary fiber."[28] In contrast, a fiber that is "isolated" or "synthetic" must first be determined by FDA to have "physiological effects that are beneficial to human health" before it can be categorized as dietary fiber in labeling. To date, FDA has approved only seven isolated or synthetic fibers as "dietary fiber,"[29] and has stated that a manufacturer who wants to declare any other non-naturally occurring fiber as a dietary fiber should submit a citizen petition that provides "scientific evidence of a beneficial physiological effect to human health" associated with the fiber.[30] But the citizen petition process − a lengthy and resource-intensive process − places a significant burden on manufacturers. CRN previously raised concerns regarding FDA's definition of dietary fiber and associated regulatory requirements in comments to the proposed rule on the Revision of the Nutrition and Supplement Facts Labels,[31] in comments responding to FDA's draft guidance document, *Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or*

[27] Food Labeling: Revision of the Nutrition and Supplements Facts Labels, 81 Fed. Reg. 33741 (May 27, 2016).

[28] 21 C.F.R. § 101.9(c)(6)(i) states the following: "'Dietary fiber is defined as non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health."

[29] *Id.* "The following isolated or synthetic non-digestible carbohydrate(s) have been determined by FDA to have physiological effects that are beneficial to human health and, therefore, shall be included in the calculation of the amount of dietary fiber: [beta]-glucan soluble fiber (as described in §101.81(c)(2)(ii)(A)), psyllium husk (as described in §101.81(c)(2)(ii)(A)(6)), cellulose, guar gum, pectin, locust bean gum, and hydroxypropylmethylcellulose."

[30] Questions and Answers for Industry on Dietary Fiber, FDA (Jan. 2017), https://www.fda.gov/food/ingredientspackaginglabeling/labelingnutrition/ucm528582.htm.

[31] CRN Comments to Food Labeling: Revision of the Nutrition and Supplement Facts Label [FDA-2012-N-1210] (Aug. 1, 2014), http://www.crnusa.org/sites/default/files/pdfs/comments-pdfs/CRN_Comments_FDA_ProposedRule-RevisionNutritionSupplementFactsLabels080114.pdf.

Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition,[32] and in comments regarding the American Bakers Association (ABA) Citizen Petition, which requests that FDA revoke the definition of dietary fiber in 21 C.F.R. § 101.9(c)(6)(i) and revert to the chemical definition of dietary fiber.[33] The requirement for petitions to demonstrate that isolated or synthetic non-digestible carbohydrates qualify as dietary fiber will put a substantial burden on the agency, as well as on manufacturers and marketers of innovative fiber products. Concurrently, the requirement will delay the marketing of an important nutrient increasingly recognized for its range of health benefits. Further, the standard of evidence detailed in the draft guidance on dietary fiber is unduly burdensome for listing an isolated or synthetic non-digestible carbohydrate as dietary fiber on product labeling.

- Available Data on Cost or Economic Impact: According to FDA's Regulatory Impact Analysis of its Nutrition and Supplement Facts Labels final rule,[34] FDA estimates that, as a result of the rule, 64,194 dietary supplement universal product codes (UPCs) would require "minor changes" to the label (i.e., one-color/printing plate change that does not require a label redesign), while 191 dietary supplement UPCs would require "major changes" to the label (i.e., multiple color/printing plate change that requires a label redesign). With the costs per labeling change estimated to range from $3,332 to $3,460, manufacturers face between $214,530,820 and $222,772,100 in labeling updates.

- Proposed Solution: Immediately stay the definition of dietary fiber and related recordkeeping requirements while addressing the issues raised in the comments that CRN prepared in response to the proposed rule on the Revision of the Nutrition and Supplement Facts Labels, in comments submitted by CRN and other organizations on FDA's draft guidance regarding dietary fiber, as well as in the ABA petition.

H. Fat Disclosures for Nutrient Content Claims Made About the Level of Dietary Fiber

Name of Regulation	Specific Requirements for Nutrient Content Claims – Fiber Claims
Type of Product or FDA Center Regulating Product	CFSAN

[32] CRN Comments to Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition; Draft Guidance for Industry [FDA–2016–D–3401] (Feb. 13, 2017), https://www.crnusa.org/sites/default/files/pdfs/comments-pdfs/FDA%20Dietary%20Fiber%20Draft%20Guidance_CRN%20Comments_13Feb2017.pdf.

[33] CRN Comments to American Bakers Association Citizen Petition [FDA-2017-P-2229-0001] (Oct. 4, 2017), https://www.crnusa.org/sites/default/files/pdfs/comments-pdfs/FDA-DietaryFiber-ABAPetition_CRNComments_4October2017.pdf.

[34] Regulatory Impact Analysis, Food Labeling: Revision of the Nutrition and Supplement Facts Labels [FDA-2004-N-0258], https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/UCM506797.pdf.

Citation	21 C.F.R. § 101.54(d)
Approved Information Collection and OMB Control Number	OMB Control No. 0910-0813

- Brief Description of Concern: 21 C.F.R. § 101.54(d) requires that when a nutrient content claim is made about the level of dietary fiber in a product, but the product does not meet the definition for "low" in total fat, the label must disclose the level of total fat per labeled serving. Recently, FDA has expressed the desire to keep nutrition labeling up-to-date, as the field of nutrition continues to evolve. Current public health recommendations focus on types of fat, rather than amount of fat, making the regulation out-of-date. In 2016, FDA published a guidance document[35] that implements enforcement discretion for use of the claim "healthy" in food labeling, based on the aforementioned line of thinking, to remove the requirement that a product must be "low" in total fat to qualify for a nutrient content claim. If the product is not "low" in total fat, it should have a fat profile makeup of predominantly mono and polyunsaturated fats. This same reasoning should be applied to the nutrient content claims regarding dietary fiber as well.

- Available Data on Cost or Economic Impact: n/a

- Proposed Solution: Revise 21 C.F.R. § 101.54(d) to remove the requirement for a total fat disclosure statement to be used in conjunction with nutrient content claims regarding dietary fiber for products that are not "low" in total fat but have a fat profile makeup of predominantly mono and polyunsaturated fats.

I. Guidance Document on the Scientific Evaluation of Health Claims

Name of Regulation	Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. § 101.14(c) and 21 U.S.C. § 343(r)(3)
Approved Information Collection and OMB Control Number	OMB Control No. 0910-0813

- Brief Description of Concern: In January 2009, FDA issued *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation on Health Claims*[36] (hereinafter "the Health Claims Guidance"), that describes the systematic science-based evaluation process the agency

[35]Guidance for Industry: Use of the Term "Healthy" in the Labeling of Human Food Products, FDA (September 2016), https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm521690.htm.

[36] Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation on Health Claims, FDA (January 2009), https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm.

uses to evaluate the totality of the current and publically available scientific evidence for a health claim, and FDA's interpretation of the Significant Scientific Agreement (SSA) standard for authorizing health claims. Despite FDA's intention to provide guidance to health claim petitioners on how the agency will "determin[e] whether there is SSA to support an authorized health claim, or credible evidence to support a qualified health claim," the information provided in the Health Claims Guidance does not reflect up-to-date best practices in the systematic review framework, and is inadequate to inform the industry about how the agency conducts systematic science-based evaluations of the strength of the evidence in an objective and consistent manner.

- Available Data on Cost or Economic Impact: n/a

- Proposed Solution: Since its issuance nine years ago, FDA has not updated the Health Claims Guidance. The scientific methodology for an evidence-based systematic review to establish causal relationship for health outcomes has progressed in recent years to enhance its transparency, consistency and objectivity, and to better leverage the strength of research synthesis and evidence integration. We request that FDA consider updating its systematic review process and methodology for health claims evaluation to keep pace with current best practices in the systematic review area, which will help enhance the transparency and objectivity of its evaluation, and ensure the industry is adequately informed and clearly understands the process and criteria applied by the agency in assessing scientific evidence and arriving to objective conclusions on health claims. Specifically, we request FDA consider the following recommendations:

    - **Consider unpublished data in the evaluation of health claims:** In the Health Claims Guidance, FDA states that it will only consider "publicly available data and written information pertaining to the relationship between a substance and disease." For a systematic review to be rigorous, unpublished data should also be considered as long as the information is pertinent for the evaluation of the health claim and meets the defined criteria for study population, endpoints, and study quality. According to the Agency for Healthcare Research and Quality's (AHRQ) *Methods Guide for Effective and Comparative Effectiveness Reviews* (2014),[37] a comprehensive literature search in a systematic review process includes both published studies as well as "grey literature." Examples of grey literature include unpublished trial data, government documents, and/or manufacturer information. AHRQ includes unpublished data in its systematic reviews to identify and overcome any bias introduced by selecting only published studies and to objectively assess reporting bias for each study. We request that FDA widen the scope of the studies and data it will evaluate for health claims by including unpublished studies and data which are identified through literature searches by the agency and/or public submissions. Further, we request that FDA consider establishing clear criteria and guidelines for the presentation and submission of unpublished proprietary data to ensure the evidence submitted has sufficient detail, adequate quality, and appropriate applicability for scientific evaluation of the targeted health claim. In addition, FDA should consider establishing guidelines for the protection of proprietary data from disclosure to the public. FDA already has a process

[37] Methods Guide for Effectiveness and Comparative Effectiveness Reviews, AHRQ (January 2014), https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-methods-guide_overview.pdf.

whereby the public can submit information as a "Confidential Submission" which will not be disclosed except in accordance with 21 CFR § 10.20. Consideration of unpublished proprietary data in claims evaluations is an accepted practice by other authoritative bodies. In the *Guidance Document for Preparing a Submission for Food Health Claims* (2009),[38] Health Canada allows applicants to submit unpublished and in-press articles in petitions, in addition to published studies. In the most recent *Scientific and technical guidance for the preparation and presentation of a health claim application* (2016)[39], EFSA also requests that all pertinent scientific data, both published and published, be submitted for review. The requested revision would allow FDA to draw a conclusion based on a comprehensive review of all the available scientific evidence.

- **Clear guidance in assessing methodological quality of studies:** In the Health Claims Guidance, FDA lists a number of factors for consideration when assessing the methodological quality of studies, such as study design, data collection, quality of statistical analysis, type of outcome measured, and study population characteristics. It is worth noting that a number of expert groups have developed more clear and robust scientific evidence quality rating systems, such as the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, the Consolidated Standards of Reporting Trials (CONSORT) statements, and the Strengthening the Report of Observational Studies in Epidemiology (STROBE) initiative. Particularly, the GRADE system has been adopted by several federal authoritative bodies, including the National Academies of Sciences, Engineering, and Medicine (NAS), AHRQ, the National Toxicology Program Office of Health Assessment and Translation (OHAT), and the USDA Nutrition Evidence Library (NEL). We request that FDA update its guidance document by providing clear guidance to the industry on how the agency intends to objectively assess and assign the quality rating of the studies for health claims evaluation. In the *Guidance Document for Preparing a Submission for Food Health Claims* (2009), Health Canada provides clear instruction on the methodology and scientific basis for petitioners to conduct quality appraisals of both intervention and observational studies. By using the tool, petitioners can easily understand what is expected by the regulatory agency, and such transparency will help eliminate questions on bias or subjectivity in the assessment.

- **Conduct meta-analyses in assessing the totality of scientific evidence for health claim authorization:** While FDA's current approach (in accordance with the Health Claims Guidance) can identify the quantity of positive and negative studies, it fails to take into consideration the size of the effect and the weight carried by different studies in the totality of evidence. Currently, the scientific community and health agencies regularly use quantitative systematic review methodologies, such as meta-analyses, to answer science-

[38] Guidance Document for Preparing a Submission for Food Health Claims, Health Canada (March 2009), https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/hpfb-dgpsa/pdf/legislation/health-claims_guidance-orientation_allegations-sante-eng.pdf.

[39] Scientific and technical guidance for the preparation and presentation of a health claim application, EFSA Panel on Dietetic Products, Nutrition and Allergies (December 14, 2016), .http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4680/epdf.

based questions. We request that FDA update its method in assessing the totality of evidence to align with the approach used by scientific groups under the U.S. Department of Human Services (US HHS). For instance, the 2015 Dietary Guidelines Advisory Committee used systematic reviews and meta-analyses evidence to answer questions in a "systematic, transparent, and evidence-based manner."[40] Another example of an authoritative scientific body using meta-analyses to answer research questions is the NAS (formerly known as the Institute of Medicine). In their assessment of different vitamin D sources and circulating levels of 25(OH)D, researchers conducted meta-analyses.[41] Other programs under US HHS, including OHAT and AHRQ, have also developed a systematic review and meta-analysis methodology to carry out evaluations of scientific evidence.[42] We request that FDA consider meta-analyses as a useful tool for quantitative systematic review when assessing the totality of evidence for health claims and qualified health claims to make the review process more objective, transparent, and consistent.

III. Food and Dietary Supplement Research

CRN recommends that FDA consider modifying its "Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards: Investigational New Drug Applications -- Determining Whether Human Research Studies Can be Conducted Without an IND (Sep. 2013)."[43]

A. Application of IND Guidance to Dietary Supplements

Name of Regulation	Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards: Investigational New Drug Applications -- Determining Whether Human Research Studies Can be Conducted Without an IND (Sep. 2013)
Type of Product or FDA Center Regulating Product	CDER, CBER, CFSAN
Citation	21 C.F.R. pt. 312

[40] Scientific Report of the 2015 Dietary Guidelines Advisory Committee, Part C. Methodology, 2015 Dietary Guidelines Advisory Committee (Feb. 2015), https://health.gov/dietaryguidelines/2015-scientific-report/05-methodology.asp.

[41] Dietary reference intakes for calcium and vitamin D, Institute of Medicine (2011), https://www.nal.usda.gov/sites/default/files/fnic_uploads//FullReport.pdf.

[42] OHAT Systematic Review, NTP Office of Health Assessment and Translation, https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html.

[43] Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards: Investigational New Drug Applications -- Determining Whether Human Research Studies Can be Conducted Without an IND [IND Guidance], FDA (Sep. 2013), https://www.fda.gov/downloads/drugs/guidances/ucm229175.pdf.

Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0014

- Brief Description of Concern: As stated in our comments to the final guidance,[44] we are concerned about the application of this guidance document, which applies the requirements for investigational new drug (IND) applications to dietary supplements and food. The procedures and requirements for an IND are not a suitable model for the study of food, dietary supplements, or their components. In addition to other concerns, as currently written, the guidance could cause many potential new dietary ingredients (NDIs) to no longer qualify as lawful NDIs because many NDI studies will now be required to be conducted under an IND.[45]

  Imposing IND requirements on supplement and food research results in unnecessary delays and restrictions without improving safety. Examples of the IND process negatively impacting research projects are well documented in a manuscript generated from a New York Academy of Sciences Symposium, *Probiotics: From Bench to Market*.[46] During the symposium, Dr. Dan Merenstein, Georgetown University, and Dr. Patricia Hibberd, Massachusetts General Hospital, shared their experiences with submitting INDs to FDA for probiotic research. Despite the researchers already complying with extensive measures to protect study participants such as, following CONSORT guidelines, receiving IRB approvals, convening data and safety monitoring boards, and registering their trials on ClinicalTrials.gov, FDA still found reason to place their clinical trials on hold. In fact, both researchers contend that these challenges push probiotic clinical trials to be conducted outside of the U.S. The researchers expressed concern that the U.S. will fall behind the rest of the world in probiotic clinical research due to unnecessary burdens associated with submitting INDs. This concern holds true for other areas of nutrition and dietary supplement research as well. CRN strongly encourages FDA to review the *Probiotics: From Bench to Market* manuscript to better understand how the

[44] CRN Comments on Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards on Investigational New Drug Applications: Determining Whether Human Research Studies Can be Conducted Without an Investigation [FDA-2010-D-0503] (April 7, 2014), https://www.crnusa.org/crn-submits-comments-docket-no-fda-2010-d-0503-guidance-clinical-investigatorssponsors-and.

[45] IND Guidance at 12. "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 for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312. For example, a clinical investigation designed to study the relationship between a dietary supplement's effect on normal structure or function in humans (e.g., guarana and maximal oxygen uptake) or to characterize the mechanism by which a dietary supplement acts to maintain such structure or function (e.g., fiber and bowel regularity) would not need to be conducted under an IND. However, a clinical investigation designed to evaluate a dietary supplement's ability to prevent osteoporosis or to treat chronic diarrhea or constipation would need to be conducted under an IND."

[46] Probiotics: from Bench to Market. Annals of the New York Academy of Sciences. 2010; Vol.1212.S1:E4 – E14, http://onlinelibrary.wiley.com/doi/10.1111/nyas.2010.1212.issue-s1/issuetoc.

IND requirements are not fit for dietary supplement or food component clinical trials and only serve as a significant obstacle to advancing science, without improving the safety of the trial design.

Additional examples are found in academia, especially for post-doctoral and graduate students engaged in complementary and alternative medicine (CAM) research. Using the example in the final IND guidance regarding the role of broccoli sprouts in cancer prevention,[47] the final IND guidance would require an academic researcher conducting such a study to dedicate a significant amount of time to filling out the IND application; conducting or paying for analytical testing to determine the characteristics, potency, purity, and stability, as well as safety, of the broccoli sprout test agent (assuming these characteristics are even determinable); and, likely engaging other professionals experienced with the IND process. All in addition to meeting the research institution's requirements. Further, even if the broccoli sprout preparation is already sold as a food or dietary supplement, the researcher would need to partner with the manufacturer to obtain information for the chemistry, manufacturing, and controls (CMC) section of the IND application or ask the manufacturer to dedicate its own resources to establishing a product master file that can be reviewed by FDA. As evidenced by the experienced researchers' testimonies published in *Probiotics: From Bench to Market*, completing an IND requires numerous hours and regulatory expertise that academic researchers in nutrition science do not commonly possess. Academic researchers wishing to explore the benefits of commonly consumed foods and dietary supplements are significantly delayed or unable to complete their research as a result.

CRN is concerned that uncertainty regarding how the IND requirements apply to supplement and food research will result in delay (and restriction) in the study of food and dietary supplements. We also share the concern of several leading nutrition and food science academics, who have stated to FDA that applying the IND requirements to the research of conventional food and dietary supplements "would have a paralyzing effect on research in the U.S. and stifle innovation and product development."[48]

The draft IND guidance, issued October 2010, was appropriately focused on drugs and biologics. However, the final IND guidance expanded FDA's interpretation of 21 C.F.R. pt. 312 to require INDs for foods and dietary supplements when the intent of a clinical research study is to examine effects on biological or physiological endpoints that are related to a disease. The specific requirements included in the IND guidance were not properly evaluated by nutrition scientists to assure that they are fit-for-purpose when applied to nutrition products that are being used in clinical research. FDA realized the significance of these challenges and initiated a partial stay on some sections of the IND guidance that apply to conventional foods and on studies intended to support health claims, but this resulted in greater confusion and concern amongst the academic research community. Requiring an IND for food and dietary supplement research introduces a significant obstacle and resource drain on clinical research

[47] IND Guidance at 16.

[48] Letter from Connie M. Weaver et al., to Janet Woodcock (Nov. 6, 2013), https://www.regulations.gov/document?D=FDA-2010-D-0503-0019.

on foods and supplements where there is no intent to market them as new drugs or make drug claims. Furthermore, the data and analysis needed to complete an IND application is tailored for drug chemical compounds rather than the complex and variable nature of dietary supplement and food components.

- Available Data on Cost or Economic Impact: The IND guidance imposes significant regulatory and cost burdens on the academic research community. At the same time, the guidance provides no additional public health benefit. The increase in time and financial resources creates an environment where nutrition research is likely to migrate to other countries that do not have burdensome regulatory requirements to conduct clinical research on dietary supplements and food, rather than stay in the U.S. and contribute to the U.S. economy.

- Proposed Solution: Exempt food and dietary supplements from the *Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards: Investigational New Drug Applications -- Determining Whether Human Research Studies Can be Conducted Without an IND*. FDA should issue separate guidance for clinical investigations of food and dietary supplements involving disease endpoints.

IV. New Dietary Ingredient Draft Guidance

CRN recommends that FDA consider modifying its "Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues (Aug. 2016)."[49]

A. Supplement-Based Approach to New Dietary Ingredient Notifications

Name of Regulation	Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues (Aug. 2016)
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 U.S.C. § 350b(a)(2)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control Nos. 0901-0606, 0910-0330

- Brief Description of Concern: This draft guidance takes a supplement-based approach to NDI notification requirements in a manner that is inconsistent with the statute and burdensome on the industry. As discussed in our comments to the 2011 draft guidance[50] and reaffirmed in

[49] Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues [NDI Draft Guidance], FDA (Aug. 2016), https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf.

[50] CRN and CHPA Comments to Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues [FDA-2011-D-0376] (Dec. 2, 2011), p. 7-14, https://www.regulations.gov/document?D=FDA-2011-D-0376-1986.

our comments to the 2016 draft guidance,[51] the plain language of section 413(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) clearly contemplates *ingredient-focused* notifications with the sole requirement that FDA receive adequate information on which any party may rely to conclude that its NDI-containing dietary supplement is reasonably expected to be safe. We appreciate that the 2016 revised draft guidance provides specific scenarios in which multiple notifications for separate dietary supplements containing the same NDI would not be required. We continue to recommend, however, that FDA permit ingredient manufacturers or distributors to submit NDI notifications that serve as the basis for establishing the safety of an NDI in a range of dietary supplements.

As dietary supplements typically contain several different dietary ingredients, requiring a separate notification for each finished dietary supplement that contains an NDI results in redundant notifications submitted by industry and reviewed by FDA, with no clear safety benefit. For example, the most recent NDI draft guidance suggests that when pre-Dietary Supplement Health and Education Act of 1994 (DSHEA) ingredients are added to a product that contains an NDI, a separate NDI notification is required. FDA suggests that the NDI notification should include a comprehensive safety review of all of the ingredients, including pre-DSHEA vitamins and minerals that have no impact on the safety profile of a dietary supplement, and how they may interact with each other and the NDI. This type of analysis is complex and not consistent with the regulation for other food ingredients.

Available Data on Cost or Economic Impact: Requiring a separate notification for each finished supplement with an NDI, rather than each NDI, results in redundant notifications that include data on the same NDI in different formulas, and also adds considerable costs to manufacturers and distributors. Developing a high-quality NDI notification is time-consuming and costly. As stated in our comments to the Office of Management and Budget, CRN disagrees with FDA's estimate that it takes 20 hours to prepare an NDI notification. We maintain that the burden on a company to extract and summarize the relevant information from its files and present it in the required format to FDA would take 100 to 350 hours.[52] According to our member companies, an NDI notification based solely on existing scientific literature could cost an entity more than $50,000, and an NDI notification that requires animal and other safety studies to be conducted could cost as much as $400,000. Requiring an NDI notification for each finished supplement containing an NDI, rather than each NDI, imposes significant costs on manufacturers and distributors and does not enhance the safety of dietary supplements.

- Proposed Solution: Consistent with our comments to the 2011 draft guidance and the 2016 draft guidance, we believe that in cases where an NDI will be combined with other dietary ingredients not specifically contemplated in a prior NDI notification, and where the safety

[51] CRN Comments to Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues [FDA-2011-D-0376] (Dec. 12, 2016), https://www.regulations.gov/document?D=FDA-2011-D-0376-1994.

[52] CRN Comments to OMB Control No. 0910-0330 [Docket No. FDA-2013-N-0878]: Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Premarket Notification for a New Dietary Ingredient (March 27, 2015).

profile of the finished product will not be altered, a separate notification is not necessary. However, should a dietary supplement utilize the NDI in a manner not contemplated by an earlier notification, or contain the NDI in combination with other ingredients that potentially impact the safety profile of the finished product, then a separate NDI notification may be necessary.

B. New Dietary Ingredient Notifications: Changes to Manufacturing Process

Name of Regulation	Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues (Aug. 2016)
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 U.S.C. § 350b(a)(2)
Approved Information Collection and OMB Control Number (as applicable)	OMB Control Nos. 0901-0606, 0910-0330

- Brief Description of Concern: Consistent with our comments to the 2011 draft guidance[53] and the 2016 draft guidance,[54] we believe that, for pre-DSHEA dietary ingredients and ingredients in the food supply that are exempt from NDI notification requirements, not all changes to the manufacturing process of an ingredient should make the ingredient an NDI. Rather, it is more efficient and effective from a regulatory and public health standpoint for each manufacturing change to be evaluated by the manufacturer on a case-by-case basis.

  There are many manufacturing changes that do not change the identity or safety profile of an ingredient. To be consistent with FDA's *Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives*, each manufacturing change should be assessed for either a change: (1) in the identity of the ingredient; or (2) to the safety of the ingredient.[55] The outcome of this assessment will determine if a separate notification is required. To further increase efficiency and save resources, CRN encourages FDA to consider a streamlined, abbreviated NDI process when manufacturing changes result in minor changes in the relative amounts or ratios of known constituents of a pre-DSHEA dietary ingredient, or for an ingredient in the food supply that is exempt from notification requirements.

- Available Data on Cost or Economic Impact: see response to Section III.B.

[53] *See* supra note 42.

[54] *See* supra note 43.

[55] Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives, FDA (June 2014), https://www.fda.gov/Food/GuidanceRegulation/ucm300661.htm.

- Proposed Solution: In the final guidance, modify Sec. IV.A.12 of the draft guidance to clarify that for pre-DSHEA dietary ingredients and ingredients in the food supply that are exempt from notification requirements that undergo a manufacturing change, notification to FDA should be required only when the change results in either a change: (1) in the identity of the ingredient (e.g., change to specifications needed to describe the ingredient); or (2) to the safety of the ingredient when consumed under the recommended conditions of use. This approach is consistent with FDA's approach to changes in the manufacturing process for other food products and ingredients.[56]

  In the final guidance, FDA should provide for an abbreviated NDI notification process that focuses on a compositional analysis that demonstrates that the manufacturing changes only result in minor changes in the relative amounts or ratios of known constituents and that no safety issues have been introduced as a result of manufacturing changes. This approach would result in a more effective and efficient NDI notification process, thereby improving public safety and promoting sound regulatory policy.

V. Food Safety Modernization Act (FSMA)

CRN recommends that FDA consider modifying or rescinding the following regulations: 21 C.F.R. pt. 121, 21 C.F.R. § 117.136, and 21 C.F.R. 1.507 which are related to (A) Intentional Adulteration Rule; and (B) the Collection of Annual Written Assurances. The basis for each of these requests is below.

A. Intentional Adulteration Rule

Name of Regulation	Mitigation Strategies to Protect Food Against Intentional Adulteration
Type of Product or FDA Center Regulating Product	CFSAN
Citation	21 C.F.R. pt. 121
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0812

- Brief Description of Concern: We support the Grocery Manufacturers Association's (GMA's) comments on 21 C.F.R. pt. 121. Specifically, FDA should re-propose the existing rule in a way that would enable manufacturers to utilize procedures already in place that have provided a high level of public health protection and that would ensure manufacturers have the flexibility needed to continuously adapt to the ever-changing nature of terrorism. Changes are also needed because the current rule requires the adoption of costly procedures that provide little if any additional public health protection. For example, the requirement to conduct a

[56] *Id.*

"vulnerability assessment for each type of food manufactured, processed, packed, or held" is burdensome and unnecessary.[57] CRN believes that permitting each facility to develop a single, facility-based "foundational food defense" would satisfy the goals of protecting the public health, providing physical access, and preventing contamination. We also agree with GMA's statement that pt. 121's interface with stakeholders was limited when compared to the other six FSMA regulations:

- The proposed rule was published December 20, 2013 with final comments due June 30, 2014.
- No Advanced Notice of Public Rulemaking (ANPRM) was issued.
- FDA never issued a re-proposed rule for stakeholder comment, as was done for the other six FSMA proposed regulations.

The last public meeting on the rule was in March 2014; there was no additional communication with stakeholders before publication of the final rule more than two years later.

- Available Data on Cost or Economic Impact: Food industry experts estimate ongoing per facility compliance costs at over $125,000 annually vs. FDA estimate of $9,000 to $16,000 and one-time initial implementation cost at over $300,000 per facility vs. FDA estimate of about $25,666. These costly mandates are highly unlikely to enhance public health protections in a meaningful and proportionate way. FDA's own economic analysis predicts a breakeven threshold of one catastrophic attack prevented "every 270-460 years."[58]

- Proposed Solution: Re-propose existing 21 C.F.R. pt. 121 with one that adds more flexibility and reduces the cost burden on industry to be commensurate with the public health benefits to be achieved. For example: permit a facility-based "foundational food defense," rather than requiring a vulnerability assessment for each type of food manufactured, processed, packed, or held. This approach would enable existing manufacturers to utilize procedures already in place, while still providing the same level of public health protection as the existing rule.

B. Collection of Annual Written Assurances

Name of Regulation	Circumstances in which the Owner, Operator, or Agent in Charge of a Manufacturing/Processing Facility is Not Required to Implement a Preventive Control (21 C.F.R. 117.136); What requirements apply when I import a food that cannot be consumed without the hazards being controlled or for which the hazards are controlled after importation? (21 C.F.R. 1.507)
Type of Product or FDA Center Regulating Product	CFSAN

[57] 21 C.F.R. § 121.130(a).

[58] Mitigation Strategies to Protect Against Intentional Adulteration, 81 Fed. Reg. 34165 at 34168 (May 27, 2016).

Citation	21 C.F.R. § 117.136 (a)(2)(ii), (3)(ii), and (4)(ii)), and a companion requirement in 21 C.F.R. § 117.137 21 C.F.R. § 1.507 (a)(2)(ii), (3)(ii), (4)(ii), and § 1.507 (b).
Approved Information Collection and OMB Control Number (as applicable)	OMB Control No. 0910-0751 OMB Control No. 0910-0752

- Brief Description of Concern: The above referenced sections require firms to annually obtain written assurances from their customers that the customer will "manufacture, process, or prepare food in accordance with applicable food safety requirements" or "obtain a similar written assurance from the entity's customer." As written, this requirement is impracticable, as it will require individual firms to annually obtain thousands, if not millions, of written assurances.

  FDA recognizes that this requirement is not practical; the agency delayed implementation for 2 years and recently announced its intent to initiate a rulemaking that takes into consideration the complex supply chain relationships and resource requirements for written assurance in the customer provisions. FDA also announced it will be exercising enforcement discretion with regard to the written assurance requirements of part 117, part 507, part 112, and the FSVP regulation until completion of that rulemaking process, to provide itself sufficient time to pursue that rulemaking.

- Available Data on Cost or Economic Impact: Based on a report from GMA, one large GMA member estimated hiring six full-time employees to manage written assurances required under Part 117. Additionally, due to the volume of assurances being managed, costs for internal information technology tools could be extensive.

Proposed Solution: CRN urges FDA to repeal each of the written assurance requirements through future rulemaking and not to replace current written assurance provisions with an alternative written assurance mechanism. Rescind the written assurance provisions in 21 C.F.R. § 117.136 (a)(2)(ii), (3)(ii), and (4)(ii)), 21 C.F.R. § 117.137; 21 C.F.R.§ 1.507 (a)(2)(ii), (3)(ii), (4)(ii), and § 1.507 (b).

* * *

Thank you for considering our comments.

Respectfully Submitted,

Douglas MacKay, N.D.
Senior Vice President, Scientific & Regulatory Affairs

Andrea W. Wong, Ph.D.
Vice President, Scientific & Regulatory Affairs

Haiuyen Nguyen
Senior Director, Scientific & Regulatory Affairs

Gisele Atkinson
Vice President, Quality & Technical Affairs

APPENDIX A

CRN suggests the following amendments to 21 CFR 111. See Section IA in the CRN comments on "Review of Existing General Regulatory and Information Collection Requirements of the Food and Drug Administration. Docket No. FDA-2017-N-5093."

21 CFR PART 111—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKAGING, LABELING, OR HOLDING OPERATIONS FOR DIETARY SUPPLEMENTS

§ 111.3 What definitions apply to this part?

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in this part. For the purpose of this part, the following definitions also apply:

Batch means a specific quantity of a dietary supplement that is uniform, that is intended to meet established specifications for identity, purity, strength, and composition, and that is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.

Lot means a batch, or a specific identified portion of a batch, that is uniform and that is intended to meet established specifications for identity, purity, strength, and composition; or, in the case of a dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is uniform and that is intended to meet established specifications for identity, purity, strength, and composition.

§ 111.30 What requirements apply to automated, mechanical, or electronic equipment?

For any automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement, you must:
(a) Design or select equipment to ensure that specifications established for the dietary supplement ~~specifications~~ are consistently met;

§ 111.70 What specifications must you establish?

(b) For each component that you use in the manufacture of a dietary supplement, you must establish component specifications as follows:
(1) You must establish an identity specification;
(2) You must establish component specifications that are necessary to help ensure that established specifications for the purity, strength and composition of dietary supplements manufactured using the components are met; and
(3) You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement that are necessary to help ensure the quality of the dietary supplement.

(c) For the in-process production:
(1) You must establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that established specifications are met for ~~the identity, purity, strength, and composition of~~ the dietary supplement~~s~~ and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement;
(2) You must provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that ~~the~~ established specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement; and
(e) For each dietary supplement that you manufacture you must establish appropriate product specifications, as necessary, for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

§ 111.75 What must you do to determine whether specifications are met?

(c) For a subset of finished dietary supplement batches that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the dietary supplement meets established product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement. To do so:
(1) You must select one or more established specifications for identity, purity, strength, composition, and the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if tested or examined on the finished batches of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product specifications (or only those product specifications not otherwise exempted from this provision by quality control personnel under paragraph (d) of this section);
(2) You must conduct appropriate tests or examinations to determine compliance with the specifications selected in paragraph (c)(1) of this section;
(3) You must provide adequate documentation of your basis for determining compliance with the specification(s) selected under paragraph (c)(1) of this section, through the use of appropriate tests or examinations conducted under paragraph (c)(2) of this section, will ensure that your finished batch of the dietary supplement meets all established product specifications for identity, purity, strength, and composition, and the limits on those types of contamination that may adulterate, or that may lead to the adulteration of, the dietary supplement; and

§ 111.80 What representative samples must you collect?

(b) Representative samples of in-process materials for each manufactured batch at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where

control is necessary to ensure that established specifications for the identity, purity, strength, and composition of dietary supplements are met, to determine whether the in-process materials meet specifications established in accordance with § 111.70(c), and as applicable, § 111.70(a);

§ 111.95 Under this subpart E, what records must you make and keep?

(b) Under this subpart E, you must make and keep the following records:
(1) The specifications established;
(2) Documentation of your qualification of a supplier for the purpose of relying on the supplier's certificate of analysis;
(3) Documentation for why meeting in-process specifications, in combination with meeting component specifications, helps ensure that the dietary supplement meets the established specifications for identity, purity, strength, and composition; and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement; and

§ 111.105 What must quality control personnel do?

(c) Reviewing and approving the documentation setting forth the basis for why meeting in-process specifications, in combination with meeting component specifications, will help ensure that established specifications for the identity, purity, strength, and composition of the dietary supplement are met;

§ 111.310 What are the requirements for the laboratory facilities that you use?
You must use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine whether:
(a) Components that you use meet specifications;

(b) In-process specifications are met as specified in the master manufacturing record; and

(c) Dietary supplements that you manufacture meet established specifications.