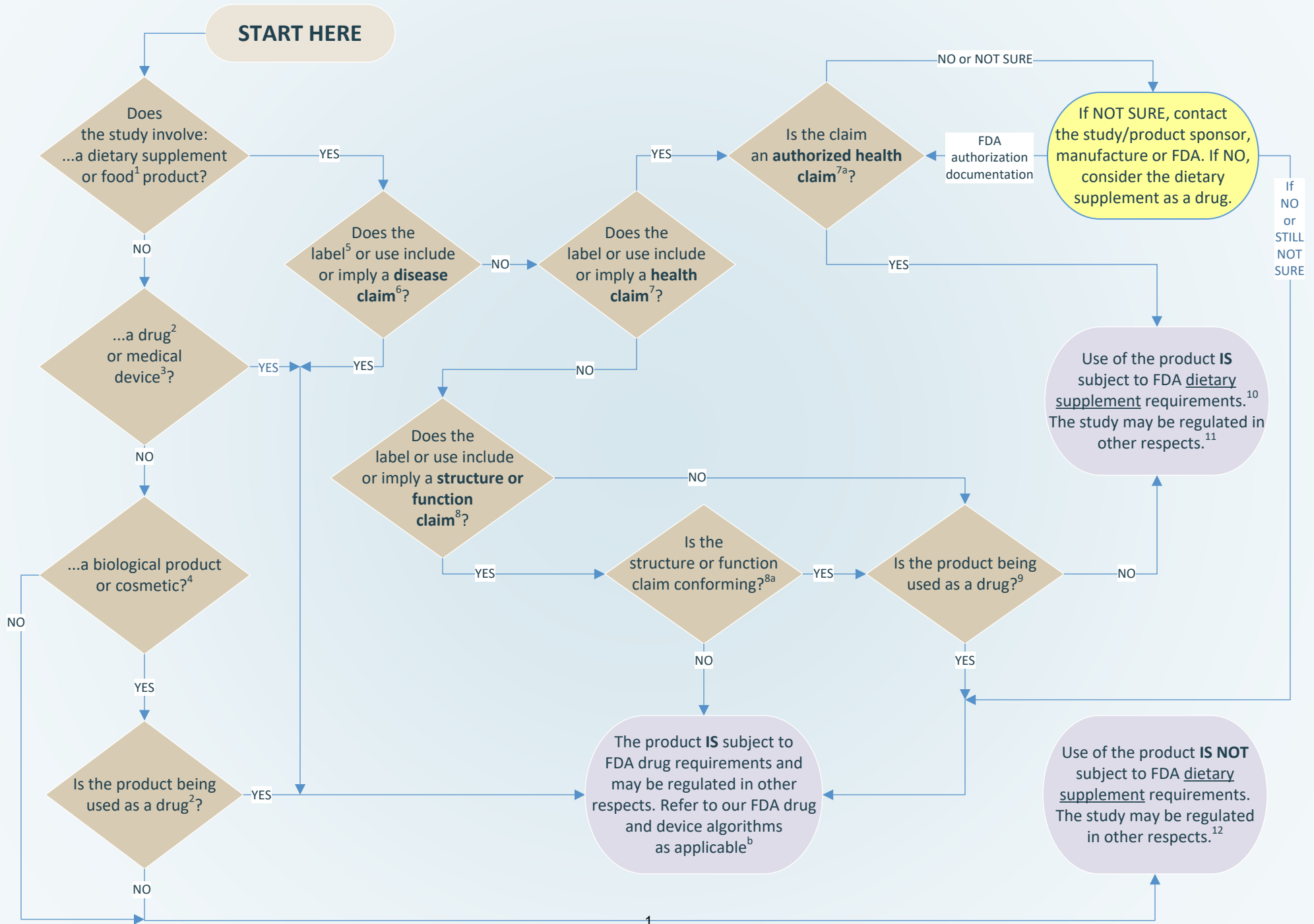


DIETARY SUPPLEMENTS (DS): Applicable FDA Regulations^a (Revised October 4, 2022)



NOTES (October 4, 2022)

^aThis algorithm applies to research that may involve U.S. Food and Drug Administration (FDA)-regulated products, particularly including use of dietary supplements. The terms research, clinical research, clinical study, study (such as used in this algorithm), and clinical investigation are deemed to be synonymous; a *clinical investigation* is defined as any experiment that involves a *test article* and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term *test article* means any drug (including a *dietary supplement*¹ that is deemed a *drug*²) for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation or the Public Health Service Act (21 United States Code of Federal Regulations (CFR) sections 56.102(c), (l)).

To locate any United States Code (USC) citation included in these Notes, see <https://www.govinfo.gov/>, browse for the United States Code, 1994-Present, and then search for the referenced Title and sections. To locate any United States Code of Federal Regulations (CFR) citation included in these Notes, see <https://www.ecfr.gov/> and search for the referenced Title and sections. The eCFR is not an official edition of the U.S. Code of Federal Regulations, but as a U.S. government online resource the eCFR provides more timely versions and ease of use.

^bFor research involving the use of drugs, devices, biological products, cosmetics and/or combination products, or any test article or product, including dietary supplements (including whether a dietary supplement may be considered a drug or a dietary supplement's use involves a disease, health and/or structure or function claim), FDA regulations specifically applicable to one or more products or test articles may apply, alone or simultaneously. As applicable, refer to our OHSP algorithms at this link: <https://www.research.fsu.edu/research-offices/ohsp/decision-trees/>; scroll down the page to the bullet "FDA-regulated Products and Test Articles".

¹ *Dietary supplement*: means—

- a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described above. . . . ;
- intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form, or if not intended for ingestion in such a form, is not represented as conventional food and is not represented for use as a sole item of a meal or of the diet and is labeled as a dietary supplement; and,
- Except when deemed a *drug*² . . . a dietary supplement shall be deemed to be a food" (21 USC 321(ff); 21 USC 350(c)(1)(B)). A conventional food is a food that is not a dietary supplement (21 USC 321(ff)(2)(B)).

A *food* is defined as "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article" (21 USC 321(f)).

² *Drug*: defined by law as "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food¹) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)" (21 United States Code (USC) section 321(g)). As indicated above in note 1 and pursuant to this definition, a dietary supplement is considered a drug if the dietary supplement (even if it is labeled as a dietary supplement) is planned for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, and such use in research must conform to all applicable drug-related FDA requirements.

³ *Medical device*: defined by law as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or . . . intended to affect the structure or any function of the body of man or other animals . . ." (21 USC §321(h)). Devices may range from simple tongue

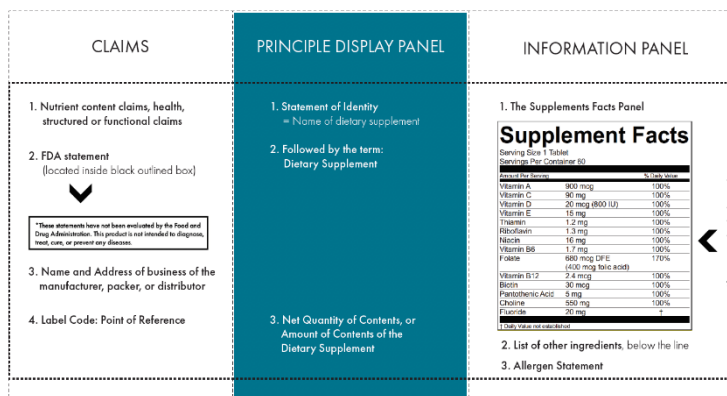
depressors and bedpans to complex programmable pacemakers, and closed loop artificial pancreas systems. Included in this definition are diagnostic devices, used to identify, interpret, measure, monitor, observe and/or characterize the nature, cause, aspect or feature of phenomenon that may be related to a health status condition, and in vitro diagnostic (IVD) products, such as reagents, test kits, and blood glucose meters, as well as diagnostic ultrasound products, x-ray machines and medical lasers. Note that software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device may also be considered a medical device. A diagnostic device is a medical device used to identify, interpret, measure, monitor, observe and/or characterize the nature, cause, aspect or feature of phenomenon that may be related to a health status condition.

⁴ The term *biological product* means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings (42 USC section 262(i)); a *cosmetic* means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap (21 USC section 321(i)).

⁵ A *label* is defined as a display of written, printed, or graphic matter upon the immediate container of any article. *Labeling* is defined as all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such an article (21 USC section 321(k), (m)). Depending on the circumstances, labeling may include packaging, product inserts, Web sites, and other promotional materials. The term *accompanying* is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc.

'Accompanying' also includes labeling that is brought together with a product after shipment or delivery for shipment in interstate commerce (see FDA's Drug Labeling page at: <https://www.fda.gov/drugs/development-resources/labeling-information-drug-products>).

Dietary supplements (including foods intended for use as dietary supplements) must be labeled in accordance with FDA regulations (21 CFR 101.36; 21 CFR 101.9(j)(6)). See the sample FDA approved labels. Note that a medical food is generally exempt from nutrition labeling requirements under certain conditions (21 CFR 101.9(j)(8)).



Supplement Facts	
Serving Size 1 Capsule	
Servings Per Container 100	
Amount Per Capsule	% Daily Value
Calories 20	
Total Fat 2 g	3%*
Saturated Fat 0.5 g	3%*
Polyunsaturated Fat 1 g	†
Monounsaturated Fat 0.5 g	†
Vitamin A 765 mcg	85%
Vitamin D 21 mcg	105%
Omega-3 fatty acids 0.5 g	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Ingredients: Cod liver oil, gelatin, water, and glycerin.

For any dietary supplement that is used in or is the object of the study, a legible copy of ALL labels and labeling must be included in the IRB submission, and a clear statement in the protocol that the dietary supplement will bear a label or labeling with at least the following information:

- Ingredients;
- Intended use;
- Safety information;
- Directions for use;
- Product information (manufacturer, production source and batch, quantity of contents in the supplement)

Studies will not be reviewed by the IRB if any labels or labeling is missing or incomplete. For FDA’s dietary supplement labeling guide, see this FDA link: <https://www.fda.gov/food/dietary-supplements-guidance-documents-regulatory-information/dietary-supplement-labeling-guide>

When a dietary supplement that is planned for use in a study will include a use that does not strictly conform to the dietary supplement’s label or labeling, then for purposes of this algorithm the use of the dietary supplement is NOT considered a use in accordance with its label or labeling. A dietary supplement, including foods intended for use as dietary supplements, are considered misbranded—and in violation of FDA regulations—if its label or labeling represents, suggests, or implies that the dietary supplement or food, because of the presence or absence of certain dietary properties, is adequate or effective in the prevention, cure, mitigation, or treatment of any disease or symptom. Information about the relationship of a dietary property to a disease or health-related condition may ONLY be provided pursuant to a FDA determination that such claims are supported by scientific evidence (21 CFR 101.14(b)).

⁶ *Disease claim*: a statement (whether included in any label or labeling associated with use of the dietary supplement or included in a study protocol or other study materials, such as consent materials), that claims to diagnose, mitigate, treat, cure, or prevent *disease* if the statement meets one or more of the criteria listed below (note that these criteria are not intended to classify as disease claims those statements that refer to the ability of a product to maintain healthy structure or function, unless the statement implies disease prevention or treatment). In determining whether a statement is a disease claim under the following criteria, FDA considers the context in which the claim is presented. The term *disease* is defined as damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunction (e.g., hypertension). A disease that result from essential nutrient deficiencies (e.g., scurvy, pellagra) is not included in this definition (21 CFR 101.93(g)(1)(2)).

A statement claims to diagnose, mitigate, treat, cure, or prevent disease if it claims, explicitly or implicitly, that a product:

- (i) Has an effect on a specific disease or class of diseases;
- (ii) Has an effect on the characteristic signs or symptoms of a specific disease or class of diseases, using scientific or lay terminology;
- (iii) Has an effect on an abnormal condition associated with a natural state or process, if the abnormal condition is uncommon or can cause significant or permanent harm;
- (iv) Has an effect on a disease or diseases through one or more of the following factors:
 - (A) The name of the product;
 - (B) A statement about the formulation of the product, including a claim that the product contains an ingredient (other than an ingredient that is an article included in the definition of “dietary supplement” under 21 U.S.C. 321(ff)(3)) that has been regulated by FDA as a drug and is well known to consumers for its use or claimed use in preventing or treating a disease;
 - (C) Citation of a publication or reference, if the citation refers to a disease use, and if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease, e.g., through placement on the immediate product label or packaging, inappropriate prominence, or lack of relationship to the product's express claims;
 - (D) Use of the term “disease” or “diseased,” except in general statements about disease prevention that do not refer explicitly or implicitly to a specific disease or class of diseases or to a specific product or ingredient; or
 - (E) Use of pictures, vignettes, symbols, or other means;
- (v) Belongs to a class of products that is intended to diagnose, mitigate, treat, cure, or prevent a disease;

- (vi) Is a substitute for a product that is a therapy for a disease;
- (vii) Augments a particular therapy or drug action that is intended to diagnose, mitigate, treat, cure, or prevent a disease or class of diseases;
- (viii) Has a role in the body's response to a disease or to a vector of disease;
- (ix) Treats, prevents, or mitigates adverse events associated with a therapy for a disease, if the adverse events constitute diseases; or
- (x) Otherwise suggests an effect on a disease or diseases.

21 CFR 101.93(g)(2).

Answer “YES” to this question if any study document (e.g., protocol, consent forms, dietary supplement or food labels) includes ANY of the above statements; otherwise answer “NO” and proceed to the next question. Note that the IRB will be the final arbiter about whether the study includes a disease claim.

⁷ A *health claim* means any claim (whether made on the label or in labeling of a dietary supplement, including a food intended for use as a dietary supplement) that expressly or by implication, including “third party” references, written statements (e.g., a brand name including a term such as “heart”), symbols (e.g., a heart symbol), or vignettes, characterizes the relationship of any dietary supplement or substance in the dietary supplement to a disease or health-related condition; however, such claims are limited to claims about disease risk reduction, and MAY NOT be a claim about the diagnosis, cure, mitigation, or treatment of a disease (other than a classical nutrient deficiency disease). Implied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the dietary supplement and a disease or health-related condition. Substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances (21 CFR 101.14(a)(1), (2)). Disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (21 CFR 101.14(a)(5)).

^{7a} *Authorized health claim* means a *health claim* that the FDA has determined via promulgated regulation that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the health claim is supported by such evidence (21 CFR 101.14(c), (d)). No expressed or implied health claim may be made on the label or in labeling for a food, regardless of whether the food is in conventional food form or dietary supplement form, unless such claim has been authorized by the FDA (21 CFR 101.14(e); 21 CFR 101.70).

If the FDA has specifically authorized and documented the authorization for a dietary supplement or food’s health claim, answer “YES” and provide the IRB with both the FDA notification of intent to issue a proposed regulation for the requested use of the health claim as well as a copy of the final rule published in the Federal Register that the health claim is authorized (21 CFR 101.70(j)(3)). If “NO” or “NOT SURE” to this question, then either (1) submit an authorization request to the FDA or obtain the FDA authorization documentation and provide the IRB with documentation of the authorization, or (2) consider deleting the health claim from all study materials. If after submitting an authorization request to the FDA, the FDA authorizes the health claim, then provide the IRB with both the FDA notification of intent to issue a proposed regulation for the requested use of the health claim as well as a copy of the final rule published in the Federal Register that the health claim is authorized (21 CFR 101.70(j)(3)). Note that a health claim that has not been so authorized will be subject to regulation as a drug (21 CFR 101.93(f)).

⁸ A *structure or function claim* is a label or labeling statement that may—subject to specific requirements, including notification to the FDA—describe the role of a nutrient or dietary ingredient that is intended to affect the structure or function in humans or that characterize the documented mechanism by which a nutrient or dietary ingredient acts

to maintain such structure or function, but only if such statement is not a *disease claim*⁶. If the label or labeling of a product marketed as a dietary supplement bears a disease claim, the product will be subject to regulation as a drug unless the claim is an *authorized health claim*^{7a} for which the product qualifies.

The following types of structure or function claims may be made:

- A statement that claims a benefit related to a classical nutrient deficiency disease and that discloses the prevalence of such disease in the U.S.;
- A statement that describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, or characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function; or
- A statement that describes the general well-being from consumption of a nutrient or dietary ingredient.

The above statements may only be made if the manufacturer of the dietary supplement has substantiation that such statement is truthful and not misleading, and the statement contains, prominently displayed and in boldface type, the following: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease” (21 USC 343(r)(6)). Any information provided to study participants must be consistent with the above; otherwise use of the dietary supplement will be considered use of a drug and will be reviewed accordingly. See note 8a below.

^{8a} Any structure or function claim-related label or labeling for a dietary supplement that is used for research purposes and which label or labeling does not conform to the requirements under footnote 8 will be considered use of a drug or other product that is not lawfully marketed in the U.S., and use of such dietary supplement will be subject to applicable FDA IND regulations. However, manufacturers’ structure or function claim-related labeling for conventional foods (i.e., not a dietary supplement) need not conform to the requirements under note 8 with regard to substantiation or disclaimer; therefore, if the structure or function claim pertains only to a conventional food, answer YES to this question and proceed to the next question.

⁹ A dietary supplement or food is being used as a *drug*² if the dietary supplement or food is intended, notwithstanding any label or labeling to the contrary, for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; such use in research must conform to all applicable drug-related FDA requirements (<https://www.fda.gov/consumers/consumer-updates/fda-101-dietary-supplements>).

¹⁰ Dietary supplement-specific requirements and references include those previously referenced, including 21 USC 350 and 341 et seq., and 21 CFR 101 et seq., specifically structure and function claims and labeling. Generally, the dietary supplement would not be considered a drug. However, if a non-conforming structure or function claim and/or labeling is made, consider the dietary supplement as a drug and refer to our drug algorithm (see note b); see also notes a, 8 and 8a to access structure or function claims and labeling requirements. To access FDA dietary supplement materials, use this link: <https://www.fda.gov/food/dietary-supplements/information-industry-dietary-supplements>.

¹¹ Aside from dietary supplement-specific requirements, other FDA regulations may apply to the use of dietary supplement for research purposes, including regulations pertaining to clinical investigations, IRB review; other label and labeling; post-marketing studies; adverse event reporting; research use of medical devices or other FDA-regulated test articles or products; CITI GCP training; etc.). See <https://www.fda.gov/drugs/guidance-compliance-regulatory-information> and <https://www.fda.gov/about-fda/fda-basics/what-does-fda-regulate>. Regardless of applicable FDA regulations, Institutional Review Board (IRB) review and other regulatory review requirements may apply in accordance with applicable laws and FSU policies.

¹² While FDA dietary supplement-specific requirements may not apply, other FDA regulations may apply to the research use of FDA-regulated test articles or products, including regulations pertaining to biological products, cosmetics and combination products; clinical investigations; IRB review; other label and labeling; post-marketing studies; adverse event reporting; CITI GCP training; etc.). See <https://www.fda.gov/drugs/guidance-compliance-regulatory-information> and <https://www.fda.gov/about-fda/fda-basics/what-does-fda-regulate>. Regardless of applicable FDA regulations, Institutional Review Board (IRB) review and other regulatory review requirements may apply in accordance with applicable laws and FSU policies.