

supplements in a manner that will prevent their adulteration. The proposal would require that your production and inprocess control system must include all requirements of this subpart and also would require your quality control unit to review and approve the production and inprocess control system. We believe that requiring a production and inprocess control system is necessary to provide consistency in producing different batches of dietary ingredients or dietary supplements and to facilitate preparing each batch.

Proposed § 111.35(c) would require that you use your quality control unit in your manufacturing, packaging, and label operations to ensure that these operations are performed in a manner that prevents adulteration and to ensure that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.

Proposed § 111.35(d) establishes requirements for any substance that may be used in a dietary ingredient or a dietary supplement. This section would require that any substance that is used be a “dietary ingredient” within the meaning of that term in section 201(ff) of the act, or, if not included with the meaning of that term, must meet the applicable statutory and regulatory requirements under section 409 of the act, or section 721 of the act (21 U.S.C. 379e) if a color additive, to ensure that the substance is safe and lawful for use in a dietary ingredient or a dietary supplement.

A “dietary ingredient” within the meaning of section 201(ff) of the act that is in, or intended for use in, a dietary supplement is exempt from the definition of “food additive” in section 201(s). Such “dietary ingredients” are not subject to the premarket approval standard for food additives under section 409 of the act. However, under section 402(f)(1) of the act, in order for a dietary ingredient or a dietary supplement not to be deemed adulterated, substances that are “dietary ingredients” that are used in the manufacture of a dietary ingredient or a dietary supplement must not present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or, if no such labeling, under ordinary conditions of use. In addition, there must be adequate information to provide reasonable assurance that a new dietary ingredient does not present a significant or unreasonable risk of illness or injury. Further, under section 402(f)(1) of the act, dietary ingredients must not be poisonous or deleterious substances within the meaning of

section 402(a)(1) of the act. Thus, manufacturers have a responsibility to ensure that the dietary ingredients and dietary supplements that they produce are not adulterated under section 402(f) of the act.

However, certain substances are not “dietary ingredients” within the meaning of section 201(ff) of the act, and thus, are not exempt under section 201(s) from regulation as a food additive under section 409 of the act. Such substances include components that are added to provide certain technical effects to the dietary supplement, such as disintegration, lubrication, or binding. In addition, such substances may include color additives that are used or intended for use to impart color to the dietary ingredient or dietary supplement. Color additives are exempt from the definition of “food additive” under section 201(s)(3) of the act and subject to approval and listing under section 721 of the act.

Proposed § 111.35(d) would require that any substance, other than a “dietary ingredient,” the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of the dietary ingredient or dietary supplement, must be:

- Authorized for use as a food additive under section 409 of the act, or
- Authorized by a prior sanction consistent with 21 CFR 170.3(l), or
- If used as a color additive, subject to a listing that, by the terms of that listing, includes the use in a dietary supplement, or
- Generally recognized as safe (GRAS) for use in a dietary ingredient or dietary supplement. Any claim that a substance is GRAS, other than a dietary ingredient within the meaning of section 201(ff) of the act, must be supported by a citation to the agency’s regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or dietary supplement, and
- Must comply with all other applicable statutory and regulatory requirements under the act.

Thus, if a color additive is used in a dietary ingredient or dietary supplement, it must be listed in Title 21 of the Code of Federal Regulations (CFR) for use in food and the listing must, by its terms, include such use in a dietary supplement. If the substance is not a color additive, it must be safe under other relevant sections of the act. Relevant considerations about the safety of a substance that may be used as an ingredient (other than a “dietary ingredient” under section 201(ff) of the

act) in a dietary ingredient or a dietary supplement would include the amounts of the substance that likely would be ingested, based on the amounts recommended or suggested in the label, or under ordinary conditions of use. Such a use may present concerns about the safety of exposure to such ingredient, based on the chronic use suggested or reasonably expected. Therefore, it is incumbent on the manufacturer to use “non-dietary ingredients,” that are safe and lawful under applicable sections of the act for such use.

As stated previously, ingredients used in dietary ingredients or dietary supplements, other than color additives, are required to be approved for use as a food additive unless excepted from the definition of a food additive under section 201(s) of the act. For example, we approved the use of sucralose as a general purpose sweetener in food, which would include its use in a dietary ingredient or dietary supplement (64 FR 43908, August 12, 1999). Some other current food additive listings that would include uses in certain types of dietary supplements include, ethyl cellulose (21 CFR 172.868) as a component of protective coatings for vitamin and mineral tablets, and hydroxypropyl cellulose (21 CFR 172.870) as a binder and disintegrator in dietary supplement vitamin or mineral tablets or wafers. If you have questions about the regulatory status of any substances that you want to use in a dietary ingredient or a dietary supplement, you are encouraged to contact CFSAN’s Office of Food Additive Safety.

We recognize that some ingredients may not be subject to section 409 of the act, food additive approval, because they are GRAS substances. For those substances that are GRAS, proposed § 111.35(d)(4) would require the manufacturer to have documentation for the basis for why such a substance, that is not a “dietary ingredient” within the meaning of section 201(ff) of the act, is approved for use or is GRAS for use in a dietary ingredient or dietary supplement.

The statute, under section 402(g)(2) of the act, provides that the Secretary may by regulation prescribe good manufacturing practices for dietary supplements. If the good manufacturing practices are not met, the dietary ingredient or dietary supplement would be adulterated under section 402(g) of the act. Under proposed § 111.35(d), substances that are not “dietary ingredients” that are used in dietary ingredients and dietary supplements must be safe and lawful to comply with CGMPs for such products. Thus, these