

activity of certain dietary ingredients used in dietary supplements, and such information would be necessary to determine an expiration date. Further, because official validated testing methods (*i.e.*, AOAC or FDA) for dietary supplements are evolving, especially for botanical dietary ingredients, few official methods are available to assess the strength of a dietary ingredient in a dietary supplement. Nevertheless, if you use an expiration date on a product, you should have data to support that date. You should have a written testing program designed to assess the stability characteristics of the dietary supplement, and you should use the results of the stability testing to determine appropriate storage conditions and expiration dates.

We invite comment on whether any final dietary ingredient and dietary supplement CGMP rule should contain provisions regarding expiration dating and the feasibility of conducting tests needed to support such dates. We also invite comments on whether to require expiration dating on certain dietary ingredients and not others, for example, require expiration dating of vitamin, mineral, and amino acid, but not of botanical dietary ingredients.

Proposed § 111.45(b) also would require your master manufacturing record to contain:

- A statement of theoretical yield of a manufactured dietary ingredient or dietary supplement expected at each point, step, or stage of the manufacturing process where control is necessary to prevent adulteration, and the expected yield when you finish manufacturing the dietary ingredient or dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is performed and material review is conducted and disposition decision is made. In this particular instance, when we refer to the manufacture of dietary ingredients, we mean to say that if you use a master manufacturing record to make dietary ingredients (that is, you make dietary ingredients rather than dietary supplements), the proposal would require the master manufacturing record to contain a theoretical yield at each point, step, or stage where control is necessary to prevent adulteration. Likewise, if you manufacture dietary supplements, the proposal would require your master manufacturing record to contain a theoretical yield at each point, step, or stage where control is necessary to prevent adulteration;

- A description of packaging and a copy of the label to be used. We propose to require such information because,

depending on the type of material you use, packaging could adulterate your dietary ingredients or dietary supplements. For example, the correct container may protect the dietary ingredient or dietary supplement from the deteriorating effects of light and if an incorrect container is used that does not provide this protection, your dietary ingredient or dietary supplement could deteriorate and could be adulterated. The description might consist of information such as the type of bottle to be used with your manufacturer's code number, if available; a description of the cap to be used with the liner specified with a manufacturer's code number, if applicable; additional materials needed in packaging; and the control number, if applicable, of the label to be used in packaging the dietary ingredient or dietary supplement. We are not aware of evidence of that dietary supplement manufacturers are using unlawful containers. Section 201(s) of the act defines "food additive" to mean any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in it's becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use). Materials used in packaging that come in contact with food or that react chemically with food, may be considered to be food contact substances or food additives. Foods and dietary ingredients may contain active substances that can react with packaging materials. Thus, FDA is proposing a CGMP requirement that manufacturer's use containers that are lawful under the act and that do not impose a risk such as leakage or the possibility of physical contamination of dietary ingredients or dietary supplements. Information on packaging and labels materials will also be helpful in case an adverse event occurs; and

- Written instructions including, but not limited to:

1. Specifications for each point, step, or stage in manufacturing the dietary ingredient or dietary supplement necessary to prevent adulteration;

2. Sampling and testing procedures;

3. Specific actions necessary to perform and verify points, steps, or stages, necessary to meet specifications and otherwise prevent adulteration, including, but not limited to, one person weighing or measuring a component and another person verifying the weight or measure and one person adding the

component and another person verifying the addition;

4. Special notations and precautions to be followed; and

5. Corrective action plans for use when a specification is not met.

You should think of the written instructions as being similar to a recipe; they should cover the important steps in your manufacturing, packaging, or holding processes, but they also should tell the reader about any special directions to follow, tests to perform, precautions to be observed, and personnel to use.

Proposed § 111.45(c) would require that you have your quality control unit review and approve each master manufacturing record and any modifications to a master manufacturing record. This provision reiterates the quality control requirements in proposed § 111.37. This proposed requirement is necessary to prevent potential problems that could result from changes to the master manufacturing record made by persons who are not qualified to assess the impact of such changes. By having your quality control unit review and approve the master manufacturing record and changes to that record, you will reduce your risk of not detecting the inclusion of an incorrect ingredient in the batch production. The quality control unit review will ensure that necessary inprocess verifications and testing instructions are included in the master manufacturing record. Further, any changes to the master manufacturing record will reduce your risk of adding the wrong component, dietary ingredient or dietary supplement or the wrong amount of a component, dietary ingredient or dietary supplement. For example, in one case, a dietary supplement manufacturer made a product that had 10 times the labeled amount of vitamin D, but did not perform any tests for vitamin D concentration as part of its review of its batch records (Ref. 23). The manufacturer discovered the superpotent batches only after State authorities had contacted them, and had to recall the product. Had the manufacturer's quality control unit reviewed the master manufacturing and batch production records earlier, the superpotent batches that represented a change from the master manufacturing record might have been detected before the product left the manufacturer, and the recall could have been avoided. The manufacturer later took steps to increase its audits of batch records, to require approval of all changes to its master