

including one product that had lot-to-lot variations of ephedrine, pseudoephedrine, and methylephedrine that exceeded 180 percent, 250 percent, and 1,000 percent, respectively. Half of the products tested differed in their label claims for ephedra alkaloid content and their actual alkaloid content. In some cases, the discrepancy exceeded 20 percent. One product did not have any ephedra alkaloids. Lot-to-lot variation in dietary ingredients is a public health problem particularly because conditions of use recommended or suggested in the labeling of dietary supplements are presumably based on the dietary supplement containing a certain amount of the dietary ingredient. If the dietary supplement contains more or less than the amount that the manufacturer represents, then the consumer does not receive the potential health benefit from the dietary supplement or is exposed to an amount that could present risk of injury or illness. The proposed rule would require manufacturers to establish controls, including master manufacturing and batch production records to ensure that they use the correct amount of the dietary ingredient to produce the dietary supplement, and that they apply the correct label to the dietary supplement.

- A private company analyzed a sample of dietary supplements and found that some dietary supplements did not contain the dietary ingredients claimed on the label (Ref. 34). The study found that 25 percent of ginkgo biloba products, 20 percent of saw palmetto, 33 percent of glucosamine, chondroitin and combined glucosamine/chondroitin, and 50 percent of SAME did not contain the dietary ingredients claimed in their product labels. The proposed rule would require manufacturers to establish and meet specifications for the identity, purity, quality, strength, and composition of dietary supplements.

Given the wide range of public health concerns presented by the manufacturing, packaging, and holding practices for dietary ingredients and dietary supplements, a comprehensive system of controls is necessary to prevent adulteration and misbranding. CGMPs are intended to establish such a comprehensive system. Manufacturers who operate in accordance with CGMPs would be less likely to distribute adulterated and misbranded dietary ingredients or dietary supplements than those who do not meet the requirements. Quality assurance will maximize the probability that unadulterated dietary supplements will reach the marketplace.

Establishing CGMP regulations for dietary supplements is only part of our broad science-based regulatory program for dietary supplements that is necessary to give consumers a high degree of confidence in the safety, composition, and labeling of dietary supplements. Aside from our CGMP efforts, we have taken other steps to protect the public health, such as:

- Reviewing claim notifications under section 403(r)(6) of the act to identify unlawful claims;
- Reviewing new dietary ingredient notifications to ensure that new dietary ingredients are reasonably expected to be safe under section 413 of the act (21 U.S.C. 350b);
- Evaluating the nutrition labeling of dietary supplements;
- Monitoring, through AERs voluntarily submitted to FDA, the occurrence of adverse events to identify potentially unsafe products; and
- Taking compliance actions against products that are adulterated or misbranded.

The CGMP regulation, if finalized, would, along with our other dietary ingredient and dietary supplement initiatives, contribute further to the protection of public health.

b. *CGMPs benefit consumers.* In addition to the public health benefits for consumers, CGMP regulations for dietary ingredients and dietary supplements will benefit consumers in other ways. Consumers should not have to wonder whether the dietary supplements they buy are adulterated or whether they contain the correct dietary ingredients or contain the dietary ingredients in the amount stated on the product's label. Consumers who purchase a product that does not contain the amount or strength listed on the label experience an economic loss because they are paying for something that they did not receive. CGMPs would require manufacturers to establish and meet specifications for identity, purity, quality, strength and composition of dietary supplements to help ensure that consumers buy dietary supplements that are not adulterated, contain the dietary ingredients declared on the product's label, and contain the amount or strength listed on the label. Therefore, CGMPs would benefit consumers.

## 2. How Will CGMP Regulations Take Into Account Technical Feasibility?

In developing this proposed rule, we were careful not to propose requirements that are not technically feasible to meet. In some areas where there has been scientific study but where the science is still evolving, the proposal recognizes the evolving state of

the science, but would give you maximum flexibility in meeting the requirement. For example, there are tests available for identity, purity, quality, strength, and composition of certain dietary ingredients or dietary supplements. Because many tests for identity, purity, quality, strength, and composition of dietary ingredient or dietary supplements have not been officially validated, the proposal would permit tests using methods other than those that are officially validated. By using the term "officially validated," we mean that the method is validated using an interlaboratory collaborative study by which a proposed method is validated by independent testing in separate laboratories under identical conditions (Ref. 35). An AOAC International (formerly the Association of Official Analytical Chemists) Official Method is an example of an officially validated method. We discuss test methods validation in more detail later in this document.

In areas where scientific study is still evolving, we did not propose specific requirements. For example, we did not propose requirements for dissolution, disintegration, bioavailability, or expiration dating. In those areas, it may be premature to propose a requirement at this time. In the preamble to this rule, we identify those areas where additional scientific study is necessary before we can propose a dietary supplement CGMP requirement. For example, we did not identify defect action levels (DALs) for dietary ingredients because there are not enough data available to identify an appropriate DAL for most dietary ingredients. Likewise, further study is needed for some dietary ingredients before dissolution, disintegration, bioavailability, expiration dating, or other quality standard requirements can be proposed.

## 3. How Can FDA Help Industry Achieve Compliance With CGMPs?

During small business outreach public meetings and in comments to the ANPRM, members of the dietary supplement industry told us that they would like our help in determining how to implement CGMP regulations for dietary ingredients and supplements. We have heard that issuing guidance documents and education and training would be helpful. We invite comment on the use of guidance documents, education, training, or other approaches and potential sources of education and training that you believe would assist industry efforts to implement the proposed CGMP regulations, if finalized as proposed.