

before introducing or delivering a dietary supplement containing a new dietary ingredient into interstate commerce. The notification must provide the basis upon which the petitioner has concluded that the dietary supplement containing the new dietary ingredient is reasonably expected to be safe. Therefore, the comments argued that procedures to identify, evaluate, and respond to potential safety concerns are not necessary in a CGMP rule.

Other comments stated that FDA should not require procedures to identify, evaluate, and consider potential safety concerns with dietary ingredients because manufacturers already have an essential and critical responsibility to substantiate the safety of the dietary ingredients they use in manufacturing a product. The comments suggested that FDA does not need to require written procedures because manufacturers must consult the generally known and generally available scientific literature to determine that a dietary ingredient is safe. Some comments suggested that, instead of FDA requiring safety evaluations, a third-party could evaluate safety concerns. Several comments suggested that manufacturers who use dietary ingredients that have little history of use in food in the United States should retain documentation concerning the dietary ingredient's safety. One comment suggested that we issue a guidance document to identify the types of acceptable "history of use" standards for dietary ingredients having little history of use in food in the United States and to describe the documentation that would be needed regarding a dietary ingredient's safety.

Although the comments focused on the safety of using particular dietary ingredients, the safety concerns described in question 6 actually consist of two concepts: (1) Is the product formulated using safe dietary ingredients; and (2) is the product manufactured, packaged, and held in a manner that would not adulterate or misbrand the product? The proposed rule focuses on safety concerns related to the latter concept. Specifically, the proposed rule focuses on the steps and processes used in the manufacturing, packaging, and holding of the product to ensure, for example, that the product has the identity, purity, quality, strength, and composition claimed and does not become adulterated or misbranded. The agency notes that no comments appeared to argue that safety issues relating to potential contamination or adulteration related to manufacturing processes are outside

CGMPs. As the comments recognize, manufacturers have an essential and critical responsibility to substantiate the safety of the dietary ingredients they use in manufacturing a product.

Section 402(g) of the act is not the only provision relevant to whether a dietary ingredient or dietary supplement may be deemed to be adulterated. Section 402(f)(1) of the act, in part, declares a dietary supplement to be adulterated if it:

- Presents a significant or unreasonable risk of illness or injury under conditions of use described in the labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;
- Is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that the dietary ingredient does not present a significant or unreasonable risk of illness or injury; or
- Is or contains a dietary ingredient that renders it adulterated under section 402(a)(1) of the act under the conditions of use recommended or suggested in the labeling. (Section 402(a)(1) of the act declares a food to be adulterated if it contains substances that are poisonous or deleterious substance that may render it injurious to health.)

Additionally, section 301(a) of the act prohibits the introduction of adulterated food into interstate commerce.

So, for a dietary ingredient or dietary supplement manufacturer to comply with sections 301(a) and 402(f)(1) of the act, it must take steps regarding potential safety concerns before it markets the product. Otherwise, if the manufacturer had no obligation to evaluate possible safety concerns before marketing a product, sections 301(a) and 402(f)(1) of the act would not make sense and the manufacturer would be acting contrary to the basic congressional intent behind DSHEA, which was to ensure that safe dietary supplements are available to consumers. For example, assume that a manufacturer wanted to market a new dietary ingredient but lacked evidence to show that it is safe. Under section 402(f)(1)(B) of the act, the manufacturer must have adequate information to provide reasonable assurance of the dietary ingredient's safety before it markets the dietary ingredient; otherwise, the dietary ingredient is adulterated under section 402(f)(1)(B) of the act, and section 301(a) of the act would prohibit its sale in interstate commerce. Thus, the manufacturer has a statutory obligation to examine safety concerns relating to the dietary

ingredients it uses before it markets the product.

The proposed CGMP rule focuses on ensuring that the manufacturer knows what it is putting in its product and is manufacturing, packaging, and holding the product in a manner that will not adulterate or misbrand the product. For example, assume that you use a particular herb as your dietary ingredient. However, there are different species of that herb. Some species are poisonous; others are not. Additionally, there are variations within the same species of herb depending on where the herbs were grown. Some variants may contain higher levels of a particular dietary ingredient or marker compound than other variants. So, how do you know whether you have the right herb (nonpoisonous species of herb intended for use) and whether it meets your specifications? CGMPs would require that you check the identity of the herbs you receive; by doing so, you would be able to tell whether you have the correct herbs, whether your herbs are poisonous, or whether they meet your specifications. In this example, the potential safety concerns involve the dietary ingredient itself rather than any issue concerning contamination which would adulterate or may lead to adulteration of the dietary ingredient, and thus, the dietary supplement which contains the dietary ingredient.

As for the comments' arguments concerning a dietary ingredient's history of use, we do not need to address history of use as part of this CGMP proposal. CGMPs focus on how a product is made under current manufacturing processes. A dietary ingredient's history of use does not provide any assurance that a particular product has the identity, purity, quality, strength, and composition that it purports to have. Further, history of use does not necessarily provide any assurance that a particular product would not pose a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling or under ordinary conditions of use.

As for those comments discussing whether manufacturers or other parties should evaluate potential safety concerns, the proposed rule would require a manufacturer to evaluate a consumer complaint to determine whether the complaint relates to good manufacturing practices. Such an evaluation would include possible hazards to health resulting from the manufacturing, packaging, or holding of a product. Nevertheless, you should note that, insofar as compliance with the act and any CGMP regulations are