

are specific to dietary ingredients and dietary supplements that establish a minimum standard of practice for manufacturing, packaging, or holding. The absence of minimum standards has contributed to the adulteration and misbranding of dietary ingredients and dietary supplements by contaminants or because manufacturers do not set and meet specifications for their products, including specifications for identity, purity, quality, strength, and composition. Thus, CGMP regulations are necessary to protect the public health because a CGMP rule would establish a minimum standard of practice for manufacturing, packaging, and holding dietary ingredients and dietary supplements.

The following examples illustrate the wide range of dietary ingredient and dietary supplement adulteration caused by manufacturing, packaging, or holding practices. The examples, although not exhaustive, demonstrate why CGMPs are necessary to protect public health:

- In 1997, we received an adverse event report (AER) regarding a young woman who had taken a dietary supplement and experienced a life-threatening abnormal heart function (Ref. 6). We investigated the AER and determined that the dietary supplement the woman consumed contained *Digitalis lanata*, a plant that can cause life-threatening heart reactions (Refs. 6 through 10). We found *D. lanata* in samples of raw material labeled "plantain" that was a dietary ingredient in one of the dietary supplement products used by this woman (Ref. 6). A nationwide listing of manufacturers indicated that 183 firms may have used the contaminated dietary ingredient in dietary supplements. The proposed CGMP regulations, had they been in effect, would have required identity and purity tests of dietary ingredients and dietary supplements and would likely have prevented the use of the *D. lanata* in these dietary supplements.

- In 1998, the American Herbal Products Association (AHPA) surveyed its members about commonly adulterated botanicals and methods useful in detecting adulteration in botanicals (Ref. 11). AHPA members identified 43 botanicals, including *D. lanata* contaminated plantain, that are commonly adulterated with contaminants, the common adulterant for each botanical, and a method for identifying the adulterant. For example, aflatoxin and mycotoxin (toxic compounds produced by certain molds) are known to contaminate certain herbal and botanical dietary supplements (Refs. 11 through 14). Under this proposed rule, a manufacturer would

have to establish specifications for botanicals that may contain toxic compounds and conduct testing to ensure that there are not toxic compounds present that may adulterate the dietary ingredient or dietary supplement.

- We have found manufacturers using nonfood-grade chemicals to manufacture dietary supplements (Ref. 15). The proposed rule would require that manufacturers establish specifications for components used in manufacturing and also would require manufacturers to establish and follow laboratory control procedures that include criteria for establishing appropriate specifications. The proposal would further require manufacturers to conduct testing to confirm that their specifications are met. These requirements, if finalized, would ensure that manufacturers establish and use appropriate criteria, such as using food-grade rather than industrial-grade chemicals, and would ensure that manufacturers conduct testing to confirm that food-grade chemicals were received from the supplier.

- Also during inspections, we have found insanitary conditions in physical plants where dietary ingredients or dietary supplements were manufactured, packaged, or held (Ref. 16). Pest infestation, building and equipment defects, and leaking pipes that drip onto dietary supplements are examples of insanitary conditions that we have found that may lead to product adulteration and could cause consumer illnesses and injuries. The proposed rule would require a manufacturer, packager, or holder to maintain its physical plant used for these activities in a sanitary condition.

- In the past, we have been involved in the recall of dietary supplements contaminated with lead (Ref. 17), salmonella (Ref. 18), *Klebsiella pneumonia* (Ref. 19), botulism (Ref. 20), and glass (Ref. 21). These contaminants can cause serious illness or injury and, in the case of lead, may result in chronic irreversible cognitive defects in children and progressive renal failure in adults. The proposed rule would require dietary ingredients and dietary supplements to be manufactured, packaged, and held in a manner that prevents adulteration, including adulteration by the contaminants such as those described.

- We also have been involved in recalls for super- and subpotent dietary supplements. Recalls of superpotent dietary supplements have included the following dietary ingredients: Vitamin A (Ref. 22), vitamin D (Ref. 23), vitamin B6 (Ref. 24), and selenium (Ref. 25). Each

of these dietary supplements contained dietary ingredient levels that could have caused serious illness or injury.

Illnesses or injuries such as nausea, vomiting, liver damage, and heart attack were reported from superpotent niacin at an average level of 452 milligrams (mg) niacin, well above the upper limit for adults of 45 mg daily (Ref. 26). Recalls for subpotent dietary supplements have included a recall of folic acid because the dietary supplement contained 34 percent of the declared level (Ref. 27). Such a product would be misbranded under section 403 of the act (21 U.S.C. 343). Folate plays a well-documented and important role in reducing the risk of neural tube defects. Neural tube birth defects, primarily spina bifida and anencephaly, cause serious lifetime debilitating injuries and disabilities, and even death. Thus, use of subpotent folic acid by women who are or may become pregnant may result in increased risk of having a child with a neural tube defect. The proposed rule would require manufacturers to establish specifications for the dietary supplement the manufacturer makes and then meet those specifications. Therefore, if the proposed rule is finalized, if the label for a folic acid supplement declares that the dietary supplement contains a certain level of folic acid, the folic acid supplement must actually contain that level, or we would consider the folic acid supplement to be adulterated under section 402(g) of the act.

- Other recalls have been necessary because of undeclared ingredients, including color additives (Refs. 28 and 29), lactose (Ref. 30), and sulfites (Ref. 31). Undeclared ingredients, such as color additives, lactose, and sulfites, may cause potentially dangerous reactions in susceptible persons (Ref. 32). The proposed rule would require manufacturers to verify that the correct labels have been applied to dietary ingredients and dietary supplements produced. The master manufacturing record would have to identify each ingredient required to be declared on the ingredient list under section 403 of the act.

- A study found that dietary ingredient content varied considerably from the declared content (Ref. 33). The study examined ephedra alkaloids in 20 herbal dietary supplements containing ephedra (*Ma Huang*) to determine their ephedra alkaloid content. This study found that norpseudoephedrine was often present in the ephedra dietary supplements. The study also observed significant lot-to-lot variations in alkaloid content for four products,