

that can cause serious adverse health effects in humans consuming the colostrum (Ref. 48). For example, if the colostrum contains drug residues, a dietary supplement containing colostrum could cause an adverse effect in a person who is allergic to the drug residue. In addition, some dietary supplements contain raw brain tissue or glands (Ref. 49) that have a high risk of containing the infective agent that causes bovine spongiform encephalopathy (BSE) if they originate from an animal infected with the disease (Ref. 37). In fact, dietary ingredients derived from different wild and domesticated animals may present microbiological and contaminant hazards that are unique to animal-derived dietary ingredients simply because the ingredient may not be amenable to physical treatments (for example, sterilization to eliminate pathogens) or there may not be appropriate methods to identify or correct a potential risk (as in the case of BSE or other transmissible spongiform encephalopathies (TSEs)).

The PHS Act is intended to prevent the introduction, transmission, or spread of communicable diseases (42 U.S.C. 264). Dietary supplements may be regulated under the PHS Act to the extent necessary to prevent the introduction, transmission, or spread of communicable diseases in intrastate and interstate commerce. Dietary supplements that contain animal-derived ingredients may carry infective agents that may not be able to be identified or that may be resistant to inactivation, as described previously. We are not aware of dietary supplement manufacturers' current procurement and handling practices of such dietary ingredients, nor the extent to which such dietary ingredients may be used. However, because the animal-derived dietary ingredients present important public health and safety issues, we are seeking comment on whether we should include in the final rule specific requirements for manufacturing, packaging, or holding animal-derived dietary ingredients. The U.S. Department of Agriculture (USDA) has imposed certain restrictions (*see* 9 CFR 94.18) on importation from certain regions of meat and edible products from certain animals. The USDA has determined that these regions present an undue risk of introducing BSE into the United States because BSE exists in the regions, because the regions have import requirements less restrictive than those that would be acceptable for import into the United States, and/or because of inadequate surveillance. Because there

is no broadly applicable or validated diagnostic test available to manufacturers to identify BSE agent infected ruminant animals or BSE agent infected materials, the agency is considering whether to require, in our final rule, specific requirements under proposed § 111.35 that are designed to prevent the use of materials derived from certain animals from regions ("BSE Countries") identified in 9 CFR 94.18. Such requirements would likely include manufacturer procedures and records and supplier certifications to ensure that a component, dietary ingredient, or dietary supplement is free of the agent of BSE. To prevent use of BSE agent-contaminated components, dietary ingredients, or dietary supplements, requirements for supplier certifications would likely include certification:

- Of the species of animal,
- Of the geographic origin of the animal,
- That no BSE was present in any of the animals in the herd from which the animal came and that none of the animals from the herd consumed mammalian-derived protein prohibited from use in ruminant feed,
- That any foreign manufacturer from which the material derived from animals was obtained:

1. Did not co-mingle material derived from animals from BSE countries with material derived from animals from non-BSE countries,

2. Established, validated, and followed plans or procedures to identify, track, and segregate material derived from animals from BSE countries from material derived from animals from non-BSE countries, and

3. Used dedicated manufacturing operations to prevent co-mingling of materials derived from animals from BSE countries with materials derived from animals from non-BSE countries. Manufacturers that rely on supplier certifications to ensure that materials derived from animals are BSE-free would likely need to verify the reliability of supplier certifications by conducting supplier audits at appropriate intervals. We invite comment on whether there are other requirements that should be considered by FDA for supplier certification or other manufacturing requirements to prevent the use of BSE agent-contaminated components, dietary ingredients, or dietary supplements. These specific requirements may be issued under the authority of the act or may need to be issued under PHS Act authority and may need to include relevant remedies available under the PHS Act. In addition, we invite

comment on whether there are animal-derived materials from BSE countries that do not present a safety concern and, if so, whether FDA should consider exempting such materials from a possible requirement that would prevent the use of animal-derived materials from BSE countries in dietary supplements and why. The agency will consider whether to include, in the final rule, provisions specifically related to the manufacture, packaging, and holding of animal-derived dietary ingredients or dietary supplements. One of the more obvious and serious hazards is the transmission of TSE (Ref. 37). We have communicated with the public and manufacturers of FDA-regulated products about appropriate steps to increase product safety and minimize the risk of products contaminated with the BSE agent. We published a notice in the **Federal Register** of August 29, 1994 (59 FR 44592), entitled "Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products" (Ref. 50). The notice, in part, published the November 1992 and December 1993 letters to manufacturers. In November 1992, we wrote to manufacturers of dietary supplements to alert them to the developing concern about TSEs in animals and Creutzfeldt-Jakob Disease in humans and recommended that they investigate the geographic source of any bovine and ovine material used in their products. We suggested that manufacturers develop plans to ensure, with a high degree of certainty, that bovine and ovine materials used in their products were not from BSE countries or from sheep flocks (foreign or domestic) infected with scrapie. In December 1993, we issued a letter recommending against the use of bovine-derived materials from cattle that resided in, or originated from, BSE countries in FDA-regulated products. In this letter, we recommended that manufacturers: (1) Identify bovine-derived materials in their products and identify all countries where the animals used to produce the materials had lived, (2) maintain traceable records for each lot of bovine materials and for each lot of FDA-regulated product using these materials, (3) document the country of origin of the live animal source of any bovine-derived materials used in the manufacture of the regulated products, and (4) maintain copies of the records identified above for FDA-regulated products manufactured using bovine-derived materials at foreign sites or by foreign manufacturers. To assure the safety and suitability for human use of animal-derived biologics, our Center for