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I. Background

A. Dietary Supplement Health and Education Act (DSHEA)

DSHEA (Pub. L. 103–417) was signed into law on October 25, 1994. DSHEA, among other things, amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 402(g) (21 U.S.C. 342(g)). Section 402(g)(2) of the act provides, in part, that the Secretary of Health and Human Services (the Secretary) may by regulation prescribe good manufacturing practices for dietary supplements. Such regulations shall be modeled after CGMP regulations for food and may not impose standards for which there is no current and generally available analytical methodology. No standard of CGMP may be imposed unless such standard is included in a regulation issued after notice and opportunity for comment in accordance with 5 CFR chapter V.

Congress enacted DSHEA to ensure consumers' access to safe dietary supplements. In the findings accompanying DSHEA, Congress stated that improving the health status of U.S. citizens is a national priority and that the use of dietary supplements may help prevent chronic diseases and maintain good health (Ref. 1). If dietary supplements are adulterated because they contain contaminants (such as filth), because they do not contain the dietary ingredient they are represented to contain (for example, a product labeled as vitamin C that actually contains niacin), or because the amount of the dietary ingredient thought to provide a health benefit (for example, folic acid to reduce the risk of neural tube defects or calcium in an amount to reduce the risk of osteoporosis) is not actually present in the supplement, then the consumer may suffer harm or may not obtain the purported health benefit from their consumption. CGMP regulations for dietary ingredients and dietary supplements will help to ensure that the potential health benefits that Congress identified as the basis for DSHEA are obtained and that consumers receive the dietary ingredients that are stated on the product label.

DSHEA directed the President to appoint a Commission on Dietary Supplement Labels (the Commission) to consider several issues under DSHEA needing clarification. The Commission was to conduct a study on, and provide recommendations for, the regulation of label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for the evaluation of such claims. In making its recommendations, the Commission was to evaluate how best to provide truthful, scientifically valid, and nonmisleading information to consumers so that such consumers could make informed and appropriate health care choices for themselves and their families. The Commission's report (Ref. 80) states that the Commission supports the efforts of industry and FDA to develop appropriate CGMPs for dietary supplements. Guidance on the type of information that a responsible manufacturer should have to substantiate statements of nutritional support and safety is also included in the Commission's report. The Commission's report states that the substantiation files should include assurance that CGMPs were followed in the manufacture of the product.

B. The Advance Notice of Proposed Rulemaking

On November 20, 1995, representatives of the dietary supplement industry submitted to FDA an outline for CGMP regulations for dietary supplements and dietary supplement ingredients. We evaluated the outline and determined that it provided a useful starting point for developing CGMP regulations. Nonetheless, we believed that the industry outline did not address certain issues that should be considered when developing a proposed rule on CGMPs for dietary ingredients and dietary supplements. For example, the industry outline did not address the need for specific controls for automatic, computer-controlled or assisted systems.

In addition to identifying a number of issues that were not included in the industry outline but on which we wanted public comment, we also recognized that other interested parties, such as consumers, other industry segments who had not participated in developing the outline, and the health care community should have an opportunity to provide comments on CGMPs for dietary supplements before we developed a proposal. Therefore, in the **Federal Register** of February 6, 1997 (62 FR 5700), we issued an advance

notice of proposed rulemaking (ANPRM) asking for comments on whether to institute rulemaking to develop CGMP regulations for dietary ingredients and dietary supplements and what would constitute CGMP regulations for these products.

The ANPRM contained the entire text of the industry outline. We also asked nine questions (which we discuss later in section II.B of this document) in the ANPRM. The questions focused on issues that the industry outline did not address such as those issues noted above. We received approximately 100 letters in response to the ANPRM. Each of those letters contained one or more comments. The comments came from consumers, consumer advocacy groups, health care professionals, health care professional organizations, industry, and industry trade associations. The majority of comments responded both to the nine questions we asked in the ANPRM and on certain provisions in the industry outline. We also address the comments on the nine questions in section II.B of this document. We discuss significant comments about certain provisions in the industry outline in our discussion of related proposed requirements.

Included with its comments to the ANPRM, the United States Pharmacopeia (USP) submitted a copy of its general chapter, "Manufacturing Practices for Nutritional Supplements," (Ref. 2) and in March/April 2002, USP proposed revisions to this general chapter to introduce provisions pertaining to botanical preparations (Ref. 82). In February 2000, we received a copy of the National Nutritional Foods Association's (NNFA) "NNFA Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements" (Ref. 3). We found that the industry outlines published in the ANPRM, the USP manufacturing practices, and the NNFA standards were useful in developing this proposed rule. We included certain provisions found in these outlines in this CGMP proposed rule. These three outlines indicate that dietary ingredient and dietary supplement manufacturers already recognize that there are basic, common steps needed to manufacture a dietary ingredient or dietary supplement that is not adulterated although, as established in the regulatory impact analysis, a large percentage of manufacturers do not follow a good manufacturing model. For example, these practices include requirements for:

- Designing and constructing physical plants that facilitate maintenance, cleaning, and proper