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I. Introduction

By themselves, requirements imposed under U.S. law provide limited assurance that dietary ingredients and dietary supplements are of adequate quality and purity for their intended purposes. New current good manufacturing practices (CGMP) regulations for dietary supplements that begin to take effect in 2008[1] require manufacturers to establish standards of identity and quality. Although these regulations represent a substantial advance, the resulting standards are not subject to public review and remain private after finalization. Further, the standards set by each manufacturer may not be uniform across the industry. Two manufacturers may each make Echinacea products, for example, but under the current law and regulation the consumer will not know the standards to which each product is held and will be unable to determine whether the two products are similar or how they differ.

This article examines the role of The United States Pharmacopeial Convention (USPC) in establishing public standards and argues that the widespread use of USPC public standards for dietary supplements and dietary ingredients, in conjunction with the new CGMPs, could help ensure the quality and consistency of these products while conserving resources both on the part of the U.S. Food and Drug Administration (FDA) and manufacturers. Reliance on USPC standards—public specifications containing tests, procedures, and acceptance criteria—would eliminate the need for repetitive development and review of validation and other data for procedures to ensure the identity and quality of a specified dietary supplement. USPC standards for identity, strength, and purity, with limits on contaminants, are generated through the credible, science-based processes of USPC's Council of Experts.[2] USPC standards, which are established by the independent experts serving

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[1] 21 C.F.R. § 111.1 *et seq*.

[2] *See* Rules and Procedures of the 2005–2010 Council of Experts § 2.06 (last revised Jan. 1, 2008) (defining the process for setting standards at USPC), *available at* http://www.usp.org/aboutUSP/governance/policies/rulesAndProcedures/ (accessed Mar. 20, 2008) [hereinafter Rules & Procedures].

on the Council of Experts,[3] generally are made available to the public for comment prior to finalization and when finalized are available publicly.[4]

In section II, this article will describe briefly the history of the USPC and the processes that the organization uses to establish quality standards for drugs, biologics, dietary supplements, food ingredients, and other healthcare items. This section also will describe the legal recognition of standards set by the USPC for drugs and biologics. Section III will discuss the USPC and its standards-setting activities for foods, including dietary supplements. Section IV will compare sections of the new CGMPs with USPC standards in specific areas, pointing out differences between the two and resulting potential safety gaps. Section V of the article will conclude with options for improving the overall "safety net" for dietary supplements through increased use and recognition of USPC standards.

II. USPC AND ITS STANDARDS

A. *USPC History*

The first Pharmacopeia of the United States was published in 1820 by a group of physicians who "sought to create a compendium of the best therapeutic products, give them useful names, and provide recipes for their preparation."[5] These practitioners were frustrated by the lack of uniformity in the medicines they prescribed and dispensed in daily life and by the resulting confusion.[6] The preface to the 1820 edition of the *United States Pharmacopoeia* (*USP*) stated that

> It is the object of a Pharmacopoeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries.[7]

The early pharmacopeias were compilations of recipes that facilitated compounding. As manufacturing gained prevalence over compounding, *USP* changed from being primarily a compendium of recipes to primarily a compendium of public standards that support testing of manufactured drugs.[8] Yet USPC has preserved its identity as an independent, science-driven, practitioner-based organization dedicated to promulgating public standards that help improve the quality of drugs and other articles.[9]

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[3] *Id.* § 2.02 ("Members of the Council of Experts, Expert Committees, and ad hoc Advisory Panels serve USP as individual experts; they do not serve any outside interest.").

[4] *Id.* § 9.06 (defining the process for providing public notice and obtaining comment on proposed standards).

[5] This gathering was the first USP Convention. 2 UNITED STATES PHARMACOPEIAL CONVENTION, UNITED STATES PHARMACOPEIA v (31st rev. 2007) [hereinafter *USP 31*].

[6] Lee Anderson & Gregory Higby, THE SPIRIT OF VOLUNTARISM—A LEGACY OF COMMITMENT AND CONTRIBUTION, THE UNITED STATES PHARMACOPEIA 1820–1995 5 (1995).

[7] United States Pharmacopeial Convention, UNITED STATES PHARMACOPEIA 17 (1st rev. 1820).

[8] *USP 31, supra* note 5.

[9] USPC CONST. art. II, § 1 (defining the membership of the USPC as including, *inter alia*, all accredited colleges and schools of medicine and pharmacy in the United States, all state medical associations and state medical societies that are members of the American Medical Association, all state pharmaceutical

B. *USPC Standards for Drugs and Foods*

USPC now publishes two compendia in a single volume: *USP* and the *National Formulary* (*NF*).[10] *NF* contains monographs for excipients, and *USP* mainly contains monographs for active pharmaceutical ingredients, finished dosage forms, biological products, dietary ingredients, dietary supplements, medical devices, and accompanying general chapters.

A monograph sets out the name and definition of an article; any packaging, storage, and labeling requirements; and a specification.[11] The specification consists of tests that are necessary to ensure the quality of that substance or product, one or more analytical procedures for each test, and acceptance criteria that effectively serve as the "goalposts" within which the substance or product must fall in order to "pass" the tests.[12] General chapters in *USP* provide "frequently cited procedures, sometimes with acceptance criteria, in order to compile into one location repetitive information that appears in many monographs."[13]

For many years, *USP* and *NF* have contained standards for items that may be considered dietary supplements, including vitamins and minerals. Since the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA),[14] USPC's Expert Committees have increasingly focused attention on developing public monographs for these products. In addition, USPC provides specifications for other ingredients that may be included in a dietary supplement in the *Food Chemicals Codex* (*FCC*), a compendium of public standards for food ingredients that USPC recently acquired from the Institute of Medicine.[15]

C. *USPC Standards-setting Processes*

USPC standards for identity, strength, and purity, with limits on contaminants, are generated by credible, science-based processes. USPC standards are established by subject-matter experts who are elected to serve as volunteers on the USPC Council of Experts and its Expert Committees.[16] The standards are in a state of continuous revision in accordance with modern scientific principles, including metrological principles articulated by international bodies such as national metrology organizations (e.g., the National Institute of Standards and Technology in the U.S. Department of Commerce) and the International Organization for Standardization (ISO), in order to stay abreast of evolving science and best measurement practices.[17]

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associations and state pharmaceutical societies that are members of the American Pharmacists Association, and numerous specific professional and scientific organizations) *available at* http://www.usp.org/aboutUSP/governance/constitutionAndBylaws/ (accessed Mar. 20, 2008).

[10] *USP 31, supra* note 5, at 3.

[11] L. Bhattacharyya *et al.*, *The Value of USP Public Standards for Therapeutic Products*, 21 Pharm. Res. 1725, 1726 (Oct. 2004).

[12] *See id*.

[13] *USP 31, supra* note 5, at v.

[14] DSHEA, Pub.L. 103-417 (Oct. 25, 1994).

[15] *See* USPC, Food Chemicals Codex (6th ed. 2008).

[16] Bylaws of the USPC, ch. VII § 1, *available at* http://www.usp.org/aboutUSP/governance/constitutionAndBylaws/ (accessed Mar. 20, 2008).

[17] *USP 31, supra* note 5. *See also* Roger L. Williams *et al.*, *Official USP Reference Standards: Metrology Concepts, Overview, and Scientific Issues and Opportunities*, 40 J. Pharma. & Biomed. Analysis 3 (Jan. 2006).

USPC's processes encourage dialogue with stakeholders during the development of public standards,[18] but USPC also has established policies and rules to protect its standards from undue influence by outside interests. Key among these policies are the conflict of interest principles that apply to USPC staff and volunteers. As the organization's Conflict of Interest Policy states, "USP employees, officers, trustees, and volunteers have an obligation to ensure that they remain free of actual or perceived conflicts of interest in the performance of their duties."[19] Expert Committee members must declare relationships, activities, and other interests that are directly and indirectly related to their standards-setting activities[20] and must excuse themselves from any final discussion and votes on issues regarding which they have a conflict of interest or the appearance of a conflict of interest.[21] Expert Committee members are reminded of these requirements at every committee meeting.[22] USPC staff not only maintain a record of all stated conflicts but also work closely with committee chairs and members to identify and evaluate potential conflicts of interest and to ensure that committee members excuse themselves from deliberations and votes as required by the Rules and Procedures of the Council of Experts.[23]

The USPC standards-setting process encourages transparency and participation. In accordance with the USPC Bylaws and the Rules and Procedures of the Council of Experts, proposed standards and proposed revisions to existing standards generally are published in draft for comment in the bimonthly *Pharmacopeial Forum* and the twice-yearly *FCC Forum,*[24] and the Expert Committee's responses to the comments received are published on the USPC website.[25] Meetings of USPC Expert Committees generally are open to the public,[26] and the schedule of committee meetings is available on the USPC website.[27] Noncommittee observers participate in many Expert Committee meetings in person or via teleconference.[28] Minutes of such open meetings are posted on the USPC website to the extent possible.[29]

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[18] *See, e.g.,* Rules & Procedures, *supra* note 2, § 12 (allowing for the creation of Stakeholder Forums and Project Teams for ongoing input from stakeholders on compendial issues).

[19] USPC Conflict of Interest Policy, *available at* http://www.usp.org/aboutUSP/governance/policies/overviewEthics.html.

[20] Rules & Procedures, *supra* note 2, § 2.06.

[21] *Id.* § 2.05(c).

[22] Email from Angela Long, Vice President, Volunteer and Organizational Affairs, USPC, to Carlos Celestino, Counsel, USPC (Oct. 3, 2008) (on file with author).

[23] *See, e.g.,* Heparin Ad Hoc Advisory Panel, USPC, Minutes of Meeting (Aug. 7-8, 2008) (on file at USPC); Parental Products—Industrial Expert Committee, USPC, Minutes of Meeting (Jan. 29, 2009) (on file at USPC) (each showing recusal of Expert Committee members due to conflict of interest).

[24] Bylaws of the USPC, *supra* note 16, ch. 7 § 11, ch. 6 § 9; Rules & Procedures, *supra* note 2, §§ 9.02, 9.06, 10.01. The *FCC Forum* is available for free online at http://forum.foodchemicalscodex.org; *Pharmacopeial Forum* is available by subscription. When there is a need for expedited publication, revisions can be published as final text without prior publication for public comment. *See* Rules & Procedures, *supra* note 2, §§ 9.02, 10.01(e). This expedited process is used sparingly. *See, e.g.,* USPC, *Hot Topics: USP Heparin Information* (last updated June 18, 2008), *at* http://www.usp.org/hottopics/heparin.html (describing the changes made to heparin monographs as a result of urgent public health needs).

[25] *See* Rules & Procedures, *supra* note 2, § 9.06(d). *E.g.,* USPC, *Commentary—2nd Supplement to USP 31–NF 26* (May 2008), *at* http://www.usp.org/pdf/EN/uspnf/2008-05-19_USP_31CommentaryFinal.pdf; USPC, *Commentary—Food Chemicals Codex (FCC) Sixth Edition* (Feb. 29, 2008), *at* http://www.usp.org/pdf/EN/fcc/2008-02-29Commentary.pdf.

[26] Rules & Procedures, *supra* note 2, § 13.01.

[27] USPC, *USP Calendar*, *at* http://www.usp.org/meetings/calendar.html (visited Oct. 3, 2008). *See also* Rules & Procedures, *supra* note 2, § 13.03.

[28] *See, e.g.*, Dietary Supplements: Information Expert Committee, USPC, Minutes of Meeting (Arpil 21, 2008) (on file at USPC); Pharmaceutical Waters Expert Committee, USPC, Minutes of Meeting (Oct. 15–16, 2007) (on file at USPC) (each noting the presence of noncommittee members).

[29] Rules & Procedures, *supra* note 2, § 13.03.

D. *USP–NF Standards and U.S. Law*

Since the passage of the Federal Food and Drugs Act in 1906, USPC's drug standards have been incorporated into federal law.[30] Today, the drug adulteration and misbranding provisions of the FDCA require compliance with *USP* and *NF*.[31] *USP* and *NF* are named as "official compendia,"[32] and all drugs—whether for human or veterinary use, whether in finished or bulk ingredient form—must either meet any standard of quality and purity defined in those compendia or clearly state how they differ.[33]

III. USPC and Foods

The FDCA ensures the quality of foods by somewhat different means than it ensures the quality of drugs. The FDCA provisions governing food do not require compliance to any compendium, likely because no compendium of food quality existed when the key federal laws were passed in 1906 and 1938.[34] The adulteration provision prohibits foods that are "filthy, putrid, or otherwise unfit for food" but does not establish any particular standard by which this determination can be made.[35] Instead, the Secretary of Health and Human Services has authority to promulgate regulations fixing and establishing for any food, under its common or usual name, "a reasonable definition and standard of identity, a reasonable standard of quality, or reasonable standards of fill."[36]

Section 403(s) of the FDCA, as implemented by DSHEA, does recognize the official compendia, including *USP* and *NF*, in relation to dietary supplements.[37] This reference is significantly different from the drug provisions that refer to *USP* and *NF* because it makes conformance to *USP* and *NF* standards optional for dietary supplements. Section 403(s) states that if *USP* or *NF* provides specifications for a dietary supplement, a dietary supplement is deemed to be misbranded if it is represented as conforming to these specifications, e.g., by using a reference to "USP" or "NF" in labeling, and fails to conform.[38]

As a practical matter, manufacturers tend to use "USP" on labeling of vitamins and minerals and not on botanical dietary supplements.[39] Vitamin and mineral manufacturers make relatively simple moieties that can readily conform to a *USP*

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[30] Federal Food and Drugs Act of 1906, 34 Stat. 768 §§ 6-7 (1906), repealed by the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 329(a).

[31] FDCA §§ 501(b), 502(g); 21 U.S.C. §§ 351(b), 352(g).

[32] FDCA § 201(j); 21 U.S.C. § 321(j).

[33] FDCA § 501(b); 21 U.S.C. § 351(b).

[34] Food Protection Committee, Food and Nutrition Board, National Academy of Sciences—National Research Council, Food Chemicals Codex Project 5-6 (Feb. 1963) (Noting that, in the development of the *FCC* after the passage of the 1958 Food Additives Amendment, "it was emphasized that while information is widespread in the scientific literature, it usually either does not completely define the compounds chemically or physically, or does not furnish adequate information on usage, purity, or methods of analysis.").

[35] FDCA § 402(a)(3); 21 U.S.C. § 342(a)(3).

[36] FDCA § 401; 21 U.S.C. § 341.

[37] FDCA § 403(s); 21 U.S.C. § 343(s).

[38] *Id.*

[39] *See*, *e.g.*, Dietary Supplement Working Group, Food Advisory Committee, FDA, Draft Report on Ingredient Identity Testing Records and Retention IV.A (June 1999) (Describing identity testing of vitamins and minerals as often following USP standards, but identity testing of botanicals can be much more complex.).

monograph.[40] These manufacturers can and do conform to *USP* standards and represent this by placing the letters "USP" on the product or ingredient label.[41]

USPC believes that the reference to the official compendia in section 403(s) may create a disincentive for manufacturers of dietary ingredients and supplements from botanical sources to use *USP* and *NF* standards. Botanical ingredients from different manufacturers may not readily conform to a single set of tests, procedures, and acceptance criteria.[42] Rather than taking the risk of being noncompliant and therefore misbranded, botanical manufacturers simply may choose not to indicate in their labeling that they are compliant with *USP* or *NF* standards. The result is that consumers have no way to tell which products meet the quality standards in *USP* and *NF*.

Yet recent events reported in the scientific literature illustrate the significant public health concerns that can result from inadequate monitoring of the quality of dietary supplements. Numerous accounts report the substitution of *Periploca sepium* in dietary supplements purporting to contain Siberian ginseng (*Eleutherococus senticosus*). Although Siberian ginseng commonly is used to support a healthy immune system, such substitution of dietary ingredients has led to toxic reactions.[43]

Products purported to contain skullcap, which is used to promote calmness and to help ease anxiety, have been substituted or have been adulterated with other members of the Lamiaceae family, particularly wild germander (*Teucrium canadense*). At least one study has reported that adulteration with wild germander resulted in hepatotoxicity for some individuals.[44]

FDA also has referred to a reported adverse event in which a raw material that was labeled as containing plantain in fact contained *Digitalis lanata,* a plant that can cause life-threatening cardiac reactions.[45] The American Herbal Products Association reported that this is a common type of botanical adulteration.[46]

In addition to the possibility that poor-quality products will harm consumers, inadequate monitoring of dietary supplement quality also increases the likelihood

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[40] Mary Ellen Camire & Mark A. Cantor, *Dietary Supplements: Nutritional and Legal Considerations*, 53 Food Tech. 87, 92 (July 1999)("[M]ineral, [sic] as well as most vitamin supplements are generally manufactured according to United States Pharmacopeia (USP) guidelines ….").

[41] Many examples of vitamins labeled as conforming to *USP* standards can be found on store shelves. *See, e.g.*, Walgreens Gold Seal Vitamin E 400 IU USP *at* http://www.walgreens.com (visited May 9, 2008); Natural Wealth Vitamin E—400 IU USP Dietary Supplement *at* http://www.americarx.com/Products/18624.html (visited May 9, 2008); CVS Vitamin C 500 mg USP Chewable Tablets *at* http://www.cvs.com/CVSApp/cvs/gateway/detail?prodid=163959 (visited May 9, 2008).

[42] *See* Presentation by Jairaj Mehta, Practical Challenges of Stability Testing on Nutraceutical Formulations at the AAPS Workshop on Pharmaceutical Stability Testing to Support Global Markets (Sept. 10, 2007), *available at* http://www.aapspharmaceutica.com/meetings/files/100/JairajMehta.pdf. *See also* Ezio Bombardelli & Valerio Bombardelli, Abstract: Approaches to Establishing the Quality of Biologically Complex Materials, *in* 4th Annual Oxford International Conference on the Science of Botanicals & American Society of Pharmacognosy: Scientific Approaches to Quality Assessment of Botanical Products (2004) ("It is very important to keep in mind that [in] changing the preparation method of a given extract very often the biological profile of the final product can change dramatically."), *available at* http://www.oxfordicsb.org/fda2004.pdf; Dean Gray, Abstract: Development of Analytical Methods for Analysis of Complex Crude Materials and Finished Products, *id*. ("The simplest of botanical preparations is a complex phytochemical collection posing a challenge to the analytical chemist.").

[43] S. McRae, *Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng*, 155 Can. Med. Assoc. J. 293 (1996); G. Koren *et al*., *Maternal ginseng use associated with neonatal androgenization*, 264 JAMA 2866 (1990); DVC Awang, *Letter: Siberian ginseng toxicity may be case of mistaken identity*, 155 Can. Med. Assoc. J. 1237 (1996).

[44] H.L. Metzman, *Monograph of* Scutellaria lateriflora, 7 J. Am. Herbalists Guild 4 (2007).

[45] 68 Fed. Reg. 12,157, 12,162 (Mar. 13, 2003).

[46] *Id*.

that dietary supplements are subpotent or lack the labeled dietary ingredient altogether. FDA has taken action against some subpotent products,[47] but ConsumerLab.com, an organization that tests dietary supplement products, often finds that tested products include less of the "active" ingredient than claimed on the label.[48] Without a legal requirement that manufacturers adhere to quality standards, consumers have no assurance that they actually are getting the dietary ingredients they believe they are buying.

IV. FDA's Dietary Supplement CGMPs and *USP* Standards

FDA's new dietary supplement CGMPs provide standards that affect the products, processes, and people involved in dietary supplement manufacturing. These standards support the overall quality of the finished dietary supplement, which must have an identity relative to a customary or usual name as well as specifications for purity, strength, and composition, with limits on contaminants.[49]

The CGMPs cover a number of areas that are important for dietary supplement quality and safety that are not addressed by *USP* standards. For instance, the CGMP regulations include specific requirements relating to recordkeeping and documentation;[50] design, suitability, and maintenance of automatic, mechanical, or electronic equipment;[51] quality control of packaging and labeling operations;[52] sampling of repackaged and relabeled products;[53] and availability of records for regulatory inspectors.[54]

Frequently, however, the CGMPs and *USP* standards address similar issues. In many of these situations, including those addressed below, the *USP* standard is more stringent or specific. Because the CGMP regulations must address every potential dietary ingredient and dietary supplement, they are—by necessity—general. *USP* monographs are specific to particular ingredients and particular products, and *USP* methods are specific to the types of dietary supplements or ingredients, e.g., botanicals or nonbotanicals; and solid oral dosage forms, solutions, or suspensions. As a result, *USP* standards can control the quality of dietary supplements in a more rigorous and targeted way.

The application of *USP* standards, including both monographs and general chapters, to dietary supplements could help ensure the safety and quality of these products for consumers. The CGMPs currently do not incorporate any *USP* methods or standards. References to *USP* methods and monographs could be added to the CGMPs as detailed in this section.

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[47] *See, e.g.*, Warning Letter from Douglas I. Ellsworth, Director, New Jersey District, FDA, to Mr. Clyde Rockoff, Universal Nutrition Services (Mar. 7, 2005) (noting that Universal Naturals Daily Caps were subpotent in vitamin A and folic acid and that Muscle-Pro 24 was subpotent in folic acid and vitamins B6, C, A, and E), *available at* http://www.fda.gov/foi/warning_letters/archive/g5236d.pdf; Warning Letter from Ballard H. Graham, Director, Atlanta District, FDA, to Victor A. Shull, Vitalabs, Inc. (Dec. 10, 1999) (noting that Chelated Mega Min High Potency Mineral Tabs were subpotent for calcium), *available at* http://www.fda.gov/foi/warning_letters/archive/m3284n.pdf.

[48] *See, e.g.*, Consumerlab.com, Press Release: Many Arthritis Supplements Lack Key Listed Ingredient (Apr. 11, 2007), *at* http://www.consumerlab.com/news/index.asp; Consumerlab.com, Press Release: Consumerlab.com Finds Some Alpha Lipoic Acid Supplements Come up Short (May 15, 2007), *id.*

[49] *See* 72 Fed. Reg. 34,752, 34,763 (June 25, 2007).

[50] *E.g.,* 21 C.F.R. §§ 111.14, 111.113(c), 111.140(b)(3), 111.605(b)-(c).

[51] *Id.* § 111.30.

[52] *Id.* § 111.127.

[53] *Id.* § 111.420.

[54] *Id.* § 111.610.

A. *Definition of Quality*

The CGMP regulations specify that "quality" means that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition, with limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under four provisions of section 402 of the FDCA:

- section 402(a)(1): if contaminants are present;
- section 402(a)(2): if it bears or contains any unintentionally added poisonous or deleterious substance;
- section 402(a)(3): if it consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food; or
- section 402(a)(4): if the dietary supplement has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth or whereby it may have been rendered injurious to health.[55]

FDA specifies that manufacturers must establish adequate controls over the production process and specifications for their product to ensure that they "consistently and reliably manufacture what [they] intend."[56] In other words,

> the manufacturer decides on the identity, purity, strength, and composition of the dietary supplement it manufactures. The focus of CGMP is on process controls to ensure that the desired outcome is consistently achieved, and not on the inherent safety of the ingredients used (which is addressed by other statutory prohibitions).[57]

Unfortunately, these CGMPs establish no minimum requirement for quality. The manufacturer is entitled to use its best judgment in establishing a standard.[58] Moreover, although the CGMPs will help ensure that one manufacturer's product is similar from batch to batch, the specifications for similar articles can vary widely from manufacturer to manufacturer.

Effectively, the CGMPs call for standards without standardization. A manufacturer may create essentially private standards for a particular dietary ingredient or dietary supplement, but the manufacturer need not make these standards public. One manufacturer's standards may bear little or no resemblance to the standards created by other manufacturers for the same ingredient or product. Thus multiple manufacturers may establish different standards of identity, strength, quality, and purity for articles that are introduced into commerce under the same name.

Use of USPC's standards for purity, strength, and composition of dietary ingredients and dietary supplements, with limits on contaminants, would provide

[55] *Id.* § 111.3; 72 Fed. Reg. 34,752, 34,762.

[56] 72 Fed. Reg. 34,752, 34,762. FDA notes that the required specification "may include a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. For example, a specification for a component may include information about the test used to verify the identity of the component and the range of test results that are acceptable." *Id.* at 34,841.

[57] *Id.* at 34,763.

[58] *See id.* at 34,763 ("For example, if you are manufacturing a dietary supplement that you know is likely to contain a contaminant, you would need to establish limits on the contaminant in your supplement, and you must design these limits to prevent the dietary supplement from being adulterated under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.").

several advantages for manufacturers, regulators, and the public because these standards are comprehensive, are publicly available, and specifically address the quality issues presented by the particular ingredient or product. For example, the *USP* monographs for botanicals provide limits or restrictions on a broad range of contaminants, including those arising from microbes, heavy metals, organic volatile impurities, and pesticides.[59]

The public nature of *USP* standards can help to ensure that dietary supplements bearing the same name are of uniform quality, which USPC believes is essential for several reasons. First, it allows customers to purchase the material that they believe they are purchasing, and thus it also enables consumers to make comparisons across products in the marketplace.[60] Second, it allows comparisons of products in clinical trials. With one quality standard applied uniformly and nationally to a particular substance, researchers can eliminate certain unknowns from their research, and, as a result, may be better able to reach conclusions about the safety and efficacy of the material.

USP standards also are specific, which allows manufacturers, regulators, and users to understand the content of the particular dietary ingredient or dietary supplement.[61] For example, *USP* contains distinct monographs for three different species and multiple preparations of Echinacea: *Echinacea angustifolia* (alone and as powdered extract), *E. pallida* (alone and as a powder and powdered extract), and *E. purpurea* (as aerial parts and as root, with—variably—availability as a powder or powder extract).[62] Because the species have differing characteristics, each monograph establishes different quality specifications.

B. *Testing for Conformance to Standards*

The CGMP regulation defines the testing that the manufacturer of a finished dietary supplement product must complete on incoming bulk ingredients and components.[63] FDA creates one standard for establishing the identity of ingredients and another for establishing all other attributes, as described in this section.

FDA requires dietary supplement manufacturers to "conduct at least one appropriate test or examination to verify the *identity* of any component that is a dietary ingredient."[64] FDA notes that a single test may be adequate in some cases, but in other cases additional tests may be necessary: "It is the responsibility of the

[59] *See, e.g.,* Powdered Red Clover Extract *in USP 31*, *supra* note 5, at 926 ("Microbial Enumeration: It meets the requirements of the tests for the absence of *Salmonella* species and *Escherichia coli*. The total aerobic microbial count does not exceed 104 [colony-forming units] per g, the total combined molds and yeasts count does not exceed 1000 cfu per g, and the enterobacterial count is not less than 1000 cfu per g …. Heavy Metals: not more than 10 µg per g. Organic Volatile Impurities: meets the requirements.").

[60] The effect, in fact, is one sought by the original founders of *USP*: "In the United States, the evil of irregularity and uncertainty in the preparation of medicines has been felt with peculiar weight.… The druggist and the medical practitioner are supplied, as their convenience may direct, with any one or more of [the varying pharmacopeias and foreign texts on the market]; and of course the character of medicinal preparation is liable to vary in every state and city of the Union. And the physician is exposed, unconsciously, to administer to his patient medicines, essentially different from those which his judgment has prescribed." Anderson, *supra* note 6, at 4-5. *See also* Bhattacharyya, *supra* note 11, at 1727.

[61] Bhattacharyya, *supra* note 11, at 1727 ("The public monograph sets the stage for the subsequent transaction, whether that transaction is between an ingredient supplier and dosage form manufacturer, wholesaler, and pharmacy, or practitioner and patient. It is crucial for the provider and purchaser to be able to confirm that the goods sold meet requisite quality standards.").

[62] *USP 31, supra* note 5, at 928-936.

[63] 21 C.F.R. § 111.75.

[64] *Id.* § 111.75(a)(1) (emphasis added).

manufacturer to determine the appropriate test(s) or examination(s) necessary to verify the identity of a dietary ingredient."[65]

Manufacturers may request an exemption from this requirement to test every incoming lot for identity.[66] A manufacturer could submit a petition to FDA naming one or more suppliers of the specific dietary ingredient for which a lesser level of testing would be required. The petition must include an alternative testing plan and information demonstrating that there would be "no material diminution of assurance compared to the assurance provided by 100 percent identity testing."[67] The manufacturer also must set forth the scientific rationale and supporting data and information supporting the proposed alternative testing.

For the safety of the public, the frequency of mix-ups in dietary ingredients during the manufacturing process must be as low as possible, and the chances of intentional adulteration of the final product must be very near zero. To these ends, USPC believes that FDA should award exemptions that are supported only by complete data sets that meet stringent quality standards.[68] Because the risk of ingredient mix-ups exists throughout the supply chain, in USPC's view such exemptions also should be granted only to manufacturers who understand and mitigate all such risks in order to ensure that the dietary ingredient exhibits the correct identity.

USPC asserts that the surest method of determining the identity of an ingredient, i.e., that it is the ingredient claimed on the label, is to test that ingredient.[69] To this end, *USP* general chapter *Good Manufacturing Practices for Dietary Supplements* <2750> requires manufacturers to conduct identity testing of all ingredients in all cases.[70] Examples of the harms that consumers suffer as a result of ingredient mix-ups or intentional adulteration are outlined above in section III.

For all attributes other than identity, the CGMPs allow a firm to rely on a certificate of analysis from the supplier of a component, if several criteria are met.[71] The firm must qualify the supplier by establishing the reliability of the supplier's certificate of analysis via confirmation of the results of the supplier's tests or examinations. The certificate of analysis must include a description of the tests or examination methods used, limits of the tests or examinations, and the actual results of the tests or examinations. The manufacturer must maintain documentation of the method for qualifying the supplier. The firm periodically must reconfirm the supplier's certificate of analysis. Finally, the manufacturer's quality control personnel must review and approve the documentation setting forth the basis for the supplier's qualification and requalification.

A requirement to test only for identity does not necessarily ensure that ingredients for dietary supplements are not contaminated, in part because the definition of one substance's "identity" is intended to ensure that the correct ingredient is present but not necessarily that all potential contaminants are absent. Unless additional testing beyond identity testing is implemented, the tester must have an idea

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[65] 72 Fed. Reg. 34,752, 34,848.

[66] 21 C.F.R. § 111.75(a)(1).

[67] 72 Fed. Reg. 34,959, 34,960 (June 25, 2007).

[68] *See* comments submitted by Susan de Mars, U.S. Pharmacopeia, to FDA 4 (Oct. 24, 2007) *available at* http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2007-N-0158.

[69] *Id*. at 2. This article uses the term "testing" to mean either testing or examination, whichever is appropriate, as in the Interim Final Rule. 72 Fed. Reg. 34,959, 34,962.

[70] *USP 31, supra* note 5, at 739.

[71] 21 C.F.R. § 111.75(a)(2)(ii); 72 Fed. Reg. 34,752, 34,835. In contrast, *USP* general chapter <2750> allows skip-lot testing of other attributes to demonstrate quality and purity, provided that identity testing is always conducted. *USP 31, supra* note 5, at 739.

of potential contaminants in order to ensure that they are absent. For instance, in response to the recent contamination of glycerin, a food ingredient, with toxic diethylene glycol (DEG), FDA recommended that importers of glycerin include a test for absence of DEG at the same time that they test glycerin to ensure that the substance is indeed glycerin.[72] Such a testing scheme does not necessarily ensure that other potential contaminants are absent. FDA also notes that excessive reliance on certificates of analysis and absence of testing contributed to the problem of glycerin contamination.[73]

For components other than dietary ingredients (so-called inactives), the CGMPs require manufacturers to confirm the identity of the component but allow the manufacturer to rely on a certificate of analysis in lieu of testing or examination.[74] A certificate of analysis also is acceptable to confirm all other attributes of the component specification.

Because the CGMPs do not define the required content of a certificate of analysis, USP general chapter *Bulk Pharmaceutical Excipients—Certificate of Analysis* <1080>, which contains requirements for a complete Certificate of Analysis for excipients, could be of significant value to the dietary supplement industry and ultimately to the public.[75] At a minimum, when reliance on a certificate of analysis is permitted by the CGMPs, USPC believes that the certificate should meet standards that will help ensure that it provides complete, reliable, and accurate information.

C. *Scientifically Valid Methods*

The CGMPs require manufacturers to ensure that they use "appropriate and scientifically valid" methods to determine whether specifications are met.[76] FDA defines a "scientifically valid method" as "one that is accurate, precise, and specific for its intended purpose. In other words, a scientifically valid test is one that consistently does what it is intended to do."[77] FDA also emphasizes that "companies should have the flexibility to adopt the method most suitable to the ingredient they are testing."[78]

FDA does not require the methods to be validated because such a requirement might prevent companies from using the most appropriate method: "Although many methods that are scientifically valid have been formally validated, other methods may not have been subject to the formal validation process, e.g., by collaborative studies using multiple laboratories, but nonetheless remain scientifically valid because they are, in fact, suitable for their intended use."[79] At the same time, the agency restates that the Proposed Rule "explicitly stated that you may use validated methods that can be found in official references, such as AOAC International, USP, and others," and "recommended you use validated methods whenever such methods are available," implicitly reaffirming these views.[80]

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[72] *See* FDA, Guidance for Industry: Testing of Glycerin for Diethylene Glycol 2 (May 2007), *available at* http://www.fda.gov/cder/guidance/7654fnl.pdf.

[73] *Id.* at 1.

[74] 21 C.F.R. § 111.75(a)(2); 72 Fed. Reg. 34,752, 34,848.

[75] *See USP 31, supra* note 5, at 517.

[76] 21 C.F.R. § 111.75(h)(1).

[77] 72 Fed. Reg. 34,752, 34,853, 34,894.

[78] *Id.* at 34,853.

[79] *Id.*

[80] *Id.*

The view of USPC and of many other international bodies, including ISO, is that analytical methods used for pharmaceuticals and dietary supplements should be validated.[81] *USP* has included a general chapter on compendial validation since 1990.[82] As staff of the Office of Dietary Supplements (ODS) in the National Institutes of Health have pointed out, "in the absence of documentation of method performance, researchers wishing to analyze a particular ingredient or product are met with an abundance of methods whose reliability is unknown or with no methods at all."[83] In fact, the U.S. Congress directed ODS to accelerate an existing method validation project because of concerns about the lack of validated, publicly available methods.[84]

D. *Performance Standards—Dissolution and Disintegration*

Performance standards like dissolution and disintegration are not part of the definition of quality in the CGMPs. Despite comments received from USPC and others, FDA declined to include dissolution and disintegration in the CGMPs because the agency believes that scientific study of this topic is still evolving and that it is premature to impose these requirements.[85] The agency notes that each manufacturer may establish requirements for dissolution, disintegration and bioavailability and "should have data to support any specifications it establishes" for these parameters.[86]

It appears that FDA's concern about the still-evolving science of dissolution and disintegration specifically relates to the correlation between performance standards and dietary ingredient absorption and bioavailability. FDA specified, for instance, that disintegration time complaints are examples of product complaints that need to be investigated because they may relate to product quality.[87]

Performance standards serve as important quality control tools that ensure batch-to-batch consistency in the manufacturing processes, whether or not the quantitative correlation between performance standards and supplement bioavailability can be demonstrated.[88] Data about dissolution and disintegration demonstrate whether the dosage form is able to release its dietary ingredients. Such release is necessary for any further absorption, distribution to the tissues, and ingredient pharmacokinet-

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[81] Joachim Ermer & Jans-Joachim Ploss, *Validation in Pharmaceutical Analysis, Part II: Central Importance of Precision to Establish Acceptance Criteria and for Verifying and Improving the Quality of Analytical Data*, 37 J. PHARMA. & BIOMED. ANALYSIS 859 (Apr. 2005). *See also* International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Harmonized Tripartite Guideline: Validation of Analytical Procedures: Text and Methodology Q2(R1) (Oct. 27, 1994), *available at* http://www.ich.org/LOB/media/MEDIA417.pdf.

[82] <1225> Validation of Compendial Procedures, *in* UNITED STATES PHARMACOPEIAL CONVENTION, UNITED STATES PHARMACOPEIA 1710 (22nd rev. 1990).

[83] Joseph M. Betz *et al.*, *The NIH Analytical Methods and Reference Materials Program for Dietary Supplements*, 389 ANALYTICAL & BIOANALYTICAL CHEM. 19 (Sept. 2007).

[84] S. REP. NO. 107–084, at 183–184 (2003).

[85] 72 Fed. Reg. 34,752, 34,851.

[86] *Id.*

[87] *Id.* at 34,798 (stating that "Complaints about disintegration time or tablet size could indicate a problem with the production and process control system that may affect the quality of the dietary supplement.").

[88] *See, e.g.*, FDA, Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms (Aug. 1997), *available at* http://www.fda.gov/cder/Guidance/1713bp1.pdf ("[I]n vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used to 1) assess the lot-to-lot quality of a drug product; 2) guide development of new formulations; and 3) ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.") (visited June 11, 2008).

ics.[89] For these reasons, *USP* requires the use of these performance tests in *Good Manufacturing Practices for Dietary Supplements* <2750>.[90]

E. *End-product Testing*

In FDA's CGMPs, conformity assessments to component and finished dietary supplement product standards are conducted via a complex series of verifications and confirmations. The CGMPs employ concepts of quality assurance and risk management, placing less weight on testing of the final product before release. The result is a reduction in the need by dietary supplement manufacturers to conduct end product testing.

The only requirement for testing a dietary supplement batch before release into the market is stated in the CGMPs at 21 C.F.R. § 111.75. This provision allows the manufacturer to use *any* established specification (test) for purity, strength, composition, or limits to serve as a proxy for all, unless one of the attributes is exempted.[91] Furthermore, the testing may be completed on a subset of batches rather than on every batch if "controls are implemented earlier than the final product stage in the manufacturing process," as long as "a statistically sound sampling and testing program" is used to select the batches for sampling.[92]

Although USPC agrees that end-product testing alone is inadequate to ensure quality,[93] end-product testing ideally provides a final check of quality, potentially including an assurance of the absence of adulterants. The requirements of quarantining and traceability outlined in the CGMPs for supplements, components, and other manufacturing materials[94] offer some protection but do not offer the same level of protection against adulterants such as DEG and melamine as end-product testing.[95]

V. Strengthening Dietary Supplement Quality with USPC Standards

USPC recognizes the substantial effort and achievement represented by the new dietary supplement CGMPs yet questions not only their adequacy in ensuring safety and quality but also the resource burden they impose on FDA and manufacturers. The regulation does not encourage the national uniformity that has been a goal of USPC since 1820. In fact, the quality requirements for dietary supplements could contribute to a situation that is similar if not identical to that of drugs in the United States in 1820.

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[89] *See, e.g.*, *id.* at 1 ("Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of in vivo performance.").

[90] *USP 31, supra* note 5, at 736.

[91] 21 C.F.R. § 111.75(c)(1), (d).

[92] 72 Fed. Reg. 34,752, 34,835. "Controls include the use of a certificate of analysis from a qualified supplier for specifications other than the identity of a dietary ingredient, and the establishment and monitoring of in-process manufacturing controls." *Id.*

[93] "Well-established principles of CGMP require process controls at each step of the manufacturing process as early in the production process as possible. Quality cannot be tested into the product only at the end.… It is not sufficient, nor effective, to rely solely on end product testing to assure the quality of the individual dietary supplement product sold to the consumer." *Id.* at 34,762.

[94] *E.g.*, 21 C.F.R. §§ 111.75(a)(2), 111.77.

[95] *See supra*, notes 72-73 and accompanying text.

USPC believes that FDA, manufacturers, and the public at large would be well served if the dietary supplement section of *USP–NF* were more broadly implemented in the United States. A variety of approaches could be taken to encourage such implementation without changing the FDCA. Among those, as noted above, is increased recognition of *USP–NF* standards for dietary supplements in the CGMP regulations.

Alternatively, Congress might choose to strengthen the misbranding provision in section 403(s) of the FDCA to require dietary supplements and dietary ingredients to conform to the standards established in *USP* or *NF* when the monograph title is used as the name of the ingredient or product. Congress also could strengthen the adulteration provisions to ensure that all dietary supplements conform to the relevant standards promulgated in *USP*. The adulteration and misbranding provisions of the Act provide powerful tools to maintain the integrity of the U.S. food and drug supply at low cost and with minimal regulatory resources. Because manufacturers risk severe penalties for introducing into or maintaining in commerce an adulterated or misbranded food or drug, they must carefully and consistently monitor their compliance with these requirements.[96]

Incorporating *USP* and *NF* more strongly into those provisions of law or into the CGMPs would conserve FDA's and manufacturers' resources. These approaches would allow FDA to reference reputable public standards that are created by a transparent and open process and that will continue to be updated as methods and products evolve. These approaches also would permit manufacturers to rely on existing validated procedures to ensure the identity of a specified dietary ingredient or dietary supplement rather than requiring each manufacturer to conduct repetitive and unnecessary method development and validation. Perhaps most importantly, the approaches proposed here would provide consumers with the important assurance that their dietary supplements are of consistently high quality—an assurance that they often do not enjoy today.

[96] *See, e.g.,* United States v. Park, 421 U.S. 658 (1975). "[T]he Act imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will insure that violations will not occur. The requirements of foresight and vigilance imposed on responsible corporate agents are beyond question demanding, and perhaps onerous, but they are no more stringent than the public has a right to expect of those who voluntarily assume positions of authority in business enterprises whose services and products affect the health and well-being of the public that supports them." *Id.* at 671 (citation omitted).