



AMA Journal of Ethics®

May 2022, Volume 24, Number 5: E382-389

MEDICAL EDUCATION: PEER-REVIEWED ARTICLE

What Should Clinicians Know About Dietary Supplement Quality?

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Abstract

Increase in dietary supplement use in the United States suggests a great need for clinicians to be aware of the range of supplements' quality parameters. Regulatory requirements exist, but specific quality parameters for each ingredient are not set by regulators. This article considers how clinicians can evaluate dietary supplement product quality, assess manufacturers' adherence to public quality standards, and encourage use of verification and certification programs.

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What Matters About Supplements' Quality

The dietary supplement industry in the United States has grown from approximately 4000 products in 1994 to between 50 000 and 80 000 products in fiscal year 2021,¹ with about 80% of US adults reporting that they take dietary supplements, according to a 2021 consumer survey.² These increases in the number of products and in consumer usage underscore the importance of clinicians understanding potential quality concerns about products represented as dietary supplements, given that the US Food and Drug Administration (FDA) does not regulate supplements as rigorously as drugs. The quality of products can be compromised by impurities, contaminants, or misidentified or substituted ingredients. Products containing drugs such as sildenafil (an active ingredient in certain erectile dysfunction drugs) or drug analogs, which are compounds whose structure and function are similar to active pharmaceutical ingredients, might also be illegally marketed as dietary supplements.

Assuming a recommendation to use a supplement is clinically indicated and evidence based, is it reasonable to expect clinicians to cultivate knowledge about which brands contain what they say they contain, recommend specific brands, and lead lab-testing efforts of what patients buy and ingest? It's important for practitioners not only to understand the quality differences, such as in purity or strength, but also to be able to apply this understanding in practice with patients. This article describes tools and

resources that clinicians can use to differentiate among products, consider select features of product quality using publicly available information, and inform patients about safe uses of dietary supplements.

Public Standards

In the United States, dietary supplements must include at least one “dietary ingredient.”³ Dietary ingredients include vitamins, minerals, herbs or other botanicals, amino acids, and dietary substances used to supplement the diet.³ The Dietary Supplement Health and Education Act (DSHEA) of 1994, which amended the Federal Food, Drug, and Cosmetic Act of 1938, sets forth the primary framework for how dietary supplements are regulated as a category of food. Under this framework, there are overarching requirements for manufacturers to ensure the quality and safety of dietary supplement products. These include a premarket notification requirement for certain new dietary ingredients, but FDA review of such notifications is not comparable to the preapproval process for drugs.⁴ Moreover, unlike the framework for drugs, conformance to a *United States Pharmacopeia-National Formulary (USP-NF)* public quality standard is voluntary for all dietary supplements. Under US law, a dietary supplement shall be deemed violative if it is represented (eg, on the product’s labeling) as conforming to a standard in the *USP-NF* but fails to so conform.⁵ This situation potentially creates a disincentive for manufacturers to claim that their dietary ingredient or supplement meets a public quality standard, such as one contained in the *USP-NF*, because the product could be deemed misbranded if it does not actually conform to the standard.

Under the DSHEA, dietary supplement manufacturers must follow current good manufacturing practice (CGMP) requirements that are intended to ensure the quality of dietary supplements. The CGMP requirements⁶ state that manufacturers must establish—for each component and for each finished dietary supplement product—specifications for identity, purity, strength, composition, and limits on contamination to ensure quality.⁷ The regulations require that manufacturers set limits for contaminants that may adulterate their products—such as microbes, microbial toxins, elemental contaminants (eg, lead, arsenic, mercury, and cadmium), and residual solvents—based on toxicological considerations. The regulations also require that appropriate tests be conducted to ensure that specifications are met and that the tests and methods used are appropriate and scientifically valid.⁸

However, the CGMP regulations do not include language specifying the tests and methods to be used or how to determine whether the tests and methods used are appropriate and scientifically valid. Accordingly, manufacturers have the flexibility to determine what tests and methods they use, including analytical methods and acceptance criteria, unless the FDA deems them inappropriate or scientifically invalid after the products have been introduced on the market (eg, if FDA discovers a problem during a routine facility inspection). Dietary supplement products manufactured from the same ingredients by different manufacturers thus could vary in quality since the manufacturers use different specifications and different tests and methods to determine whether those specifications are met. Dietary supplements that do not meet specifications as required by CGMP regulations are considered violative⁹; however, the FDA can generally only make such a determination after the products are on the market, and dietary supplement products on the market are not routinely tested by the FDA to determine whether product specifications are met.

Overall, the characteristics of the current regulatory framework for dietary supplements allow variability in quality specifications for comparable products and thus can contribute to a lack of consistency and transparency in product quality.

Contamination and Misidentification

Dietary supplements can contain impurities and contaminants in excess of levels considered acceptable for human use and can contain misidentified or substituted ingredients. The consequences of quality assurance failures can range from no noticeable or measurable effects to harms of varying severity (eg, from heavy metals in a product that can damage internal organs or increase risk of cancer¹⁰). Manufacturers' adherence to public quality standards can help address these quality concerns and help ensure dietary supplements' consistency and quality.

*Impurities and contaminants.*¹¹ Since dietary supplements are typically taken chronically, exposure to impurities and contaminants can be insidious over time. One study of 138 dietary supplements—including alfalfa, echinacea, garlic, ginger, ginkgo, St John's wort, and several vitamins and minerals—found microbial contamination ranging from low levels to higher levels.¹² Furthermore, antibiotic-resistant bacteria have been detected at low levels in various products (eg, those containing garlic, onion, and turmeric).^{13,14} A fatal case has also been reported of stomach-intestine mucormycosis in a premature infant following the infant's ingestion of a dietary product contaminated with a *Rhizopus* species (mold).¹⁵

Ingredient misidentification or substitution. Public standards can help manufacturers set appropriate specifications for identity that would enable a misidentification or substitution to be detected. Accidental substitution of ingredients can occur when ingredients with similar common names or close morphological characteristics are misidentified. For example, American black cohosh (*Actaea racemosa*) is often replaced by other Asian *Actaea* species, which can lead to liver toxicity.¹⁶ Intentional substitution of an inferior ingredient can occur when the authentic ingredient is expensive or in short supply. In some cases, the adulterants are potential allergens, such as contamination of grape seed extract with peanut skin extract.¹⁷ A recent analysis of ginseng products globally found that different species of ginseng or different parts of the ginseng plant were substituted in 24% of dietary supplements.¹⁸ Examples of economically motivated adulteration are the addition of ubiquitous flavonoids to ginkgo extract¹⁹ and the addition of dyes to bilberry extracts.²⁰ These examples of adulteration can be detected using appropriate analytical methods, such as those included in public standards.²¹

Appropriate analytical test methods are also important for preventing substitution of nonbotanical ingredients. In a recent illustrative case, a certificate of analysis was provided by a supplier positively identifying the product as L-citrulline, but it was found that affected batches actually contained N-acetyl-leucine.²² According to the certificates, the manufacturer had used a nonspecific titration-based method for testing. A more discriminating method, such as one based on high-performance liquid chromatography (HPLC), as described in the *USP-NF* dietary ingredient monograph for L-citrulline, could have been used to discriminate L-citrulline from other closely related amino acids—namely, N-acetyl-leucine and arginine. However, use of such a method is not specifically required under the CGMP regulations for dietary supplements.

Products purporting to be dietary supplements. Another major concern is products marketed as dietary supplements that do not meet the statutory definition of a dietary

supplement, often because the product contains an approved drug or drug analog(s) or does not include any dietary ingredients. In recent years, potentially harmful substances have been found in products promoted to enhance weight loss, sexual function, and athletic performance, including bodybuilding.²³ Specifically, certain dietary supplement products tested by the FDA have been found to contain the drugs sildenafil or sibutramine or to contain steroids or other potentially hazardous substances.²⁴ Adverse consequences of ingesting these products include cardiac symptoms, such as palpitations, chest pain, or tachycardia,²⁵ and other reported adverse events.^{26,27,28} The USP has published public standards on techniques that can be used to detect some of the undeclared substances that may be found in products marketed as dietary supplements.²⁹

When clinicians consider dietary supplement quality, they should be aware that not all products marketed as dietary supplements meet the legal definition of a dietary supplement.³ The FDA maintains a list of tainted products marketed as dietary supplements dating back to 2007,³⁰ which, as of December 2021, contained 1087 products. According to the FDA, this list only includes a small fraction of the potentially hazardous products with hidden ingredients marketed to consumers on the internet and in retail establishments.³⁰

Resources for Clinicians

It is important for clinicians to ask their patients about dietary supplement intake when discussing current medication usage. Patients often consume dietary supplements without consulting clinicians and frequently do not report dietary supplement intake unless specifically asked.³¹ Asking about supplement use is vital when patients are taking prescription medicines because harmful medication-supplement interactions could occur.³² Additionally, it is important for clinicians to be aware of dietary supplement quality in order to provide appropriate care and identify adverse events. A variety of resources can be used by clinicians to increase their familiarity with dietary supplements and help them differentiate among dietary supplements with regard to quality.

USP-NF public quality standards for dietary supplements. USP publishes its official public quality standards for drugs, excipients, and dietary supplements in the *USP-NF* and publishes food ingredient standards in the *Food Chemicals Codex*. Physical reference standards, which are highly characterized specimens, are used in conjunction with the monograph methods to verify that a product and its ingredients can pass tests indicating their adherence to quality standards. In the *USP-NF*, there are more than 800 dietary supplement-related documentary standards (including standards that apply to ingredients, products, and classes of ingredients or products) and approximately 200 physical reference standards. These standards provide scientifically valid analytical methods and evidence-based acceptance criteria to determine identification, composition, and limits on contaminants for dietary ingredients and dietary supplement products. Clinicians can recommend that patients look for dietary supplements that are marketed as conforming to a public standard, which may be indicated on the label.³³

The *USP Dietary Supplements Compendium (DSC)*, which provides a comprehensive set of quality standards related to dietary supplements, also contains over 100 summary admission evaluations for a variety of dietary ingredients. Admission evaluations are comprehensive literature reviews that present a dietary ingredient's known public health and safety profile, including the ingredient's chemistry, typical intake levels, potential

adulterants or contaminants, clinical trial and toxicological data, and potential adverse interactions.^{34,35} The DSC's admission evaluations can serve as a unique resource for clinicians and retailers to help them evaluate appropriate usage and potential risks of these products for patients or consumers.

Quality verification and certification programs for dietary supplements. Verification and certification programs for dietary supplements and dietary supplement ingredients can be used by manufacturers to help ensure their products' quality. These programs also serve as another tool to help consumers make decisions about dietary supplements and provide additional information for clinicians to consider regarding dietary supplement quality.³⁶ The USP, for example, provides a verification service program for dietary supplements and other products.³⁷ The program involves annual CGMP audits; evaluation of quality procedures with test methods for identity, purity, strength/composition, and contaminants; and product testing for conformance to specifications. Programs are also offered by other organizations.³⁸

Other resources for dietary supplement information. There are many other resources that can provide useful information on dietary supplements for clinicians. The National Institutes of Health Office of Dietary Supplement Programs³⁹ and the FDA's Office of Dietary Supplement Programs⁴⁰ provide informative tools and resources. Many resources are also available from the Dietary Supplements Quality Collaborative, which is a multistakeholder, cross-sector collaborative with a mission "to advance the quality and safety of products marketed as dietary supplements in the United States in the interest of protecting public health."⁴¹

Conclusion

As dietary supplement use increases in today's market, it is imperative to ensure supplements' quality. Clinicians should be aware of quality differences that may affect dietary supplements. By gaining knowledge about resources and tools that help identify quality dietary supplements—for example, meeting public standards and use of verification programs—clinicians can help their patients select appropriate products.

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Citation

AMA J Ethics. 2022;24(5):E382-389.

DOI

10.1001/amajethics.2022.382.

Conflict of Interest Disclosure

All the authors are employees of the United States Pharmacopeial Convention.

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