HHS Public Access

Author manuscript

Crit Rev Food Sci Nutr. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Crit Rev Food Sci Nutr. 2020 ; 60(2): 298–309. doi:10.1080/10408398.2018.1524364.

Current regulatory guidelines and resources to support research of dietary supplements in the United States

Regan L. Bailey

Department of Nutrition Science, Purdue University, , West Lafayette, Indiana 47907, USA

Abstract

The U.S. Dietary Supplement Health and Education Act (DSHEA) established the regulatory framework for dietary supplements as foods through the Food and Drug Administration (FDA). DSHEA outlined the legal definition, labeling requirements, and process for adverse event reporting for dietary supplements. FDA also issued formal guidance on current Good Manufacturing Practice to ensure that processes for preparation, packaging, labeling, and storage of supplements and ingredients are documented and meet specifications to ensure purity, composition, and strength. However, efficacy of dietary supplements is not required under U.S. law. Despite regulations to improve the marketplace, many challenges remain; as a result, the quality and safety of products available can be highly variable, especially for botanical and herbal products. The ability of regulators to successfully carry out their mission is hampered by the sheer number of products and manufacturing facilities and a lack of analytical methods for all ingredients and products in the marketplace, this is especially difficult for herbal and botanical dietary supplements. Safety issues continue to exist such as adulteration and contamination, especially with specific product types (i.e. body building, sexual enhancement). Thus, a need remains for continued efforts and improved techniques to assess the quality of dietary supplements, especially with regard to purity, bioavailability, and safety. This review will highlight the existing American regulatory framework for dietary supplements and will describe the remaining regulatory barriers to ensuring that safe and high-quality dietary supplements are offered in the marketplace.

Keywords

Dietary supplements; good manufacturing practices; quality; regulation; safety

Introduction

The global dietary supplement marketplace is valued at more than 130 billion USD and has consistently been growing for more than 3 decades (Zion Market Research 2017). The size and complexity of the dietary supplement market is highlighted by the fact that the United States (U.S.) Food and Drug Administration (FDA) estimates that there are more than 85,000 dietary supplement products currently available in the U.S. alone (Cohen 2012;

CONTACT Regan L. Bailey, reganbailey@purdue.edu, Department of Nutrition Science, Purdue University, 700 West State Street, West Lafayette, IN, 47907, USA.

Dwyer, Coates, and Smith 2018). According to National Health and Nutrition Examination Survey (NHANES) data, dietary supplements are widely used, with approximately half of U.S. adults and one-third of children reported using them (Bailey et al. 2011; Bailey, R. L., J. J. Gahche, P. E. Miller, et al. 2013; Bailey, R. L., J. J. Gahche, P. R. Thomas et al. 2013; Gahche et al. 2011; Kantor et al. 2016; Jun et al. 2018). Furthermore, 12% of adults who used dietary supplements reported taking at least five different products (Cowan et al. 2018). Although their use has slightly declined over the past several years, multivitamin/mineral supplements (MVMs) are the most commonly used class of products, with approximately one-third of adults in the NHANES survey reporting their use (Kantor et al. 2016). Given the multitude of types and number of dietary supplements that are available on the market, it is important that healthcare professionals, researchers, and consumers understand the governmental and voluntary regulatory framework surrounding the manufacturing and marketing of dietary supplements, including the strengths and weaknesses within the existing framework (Wallace 2015).

The primary challenge in regulating dietary supplements is the lack of international consensus on how this category of products is defined; standards that ensure quality and integrity do not exist in the global context (Dwyer, Coates, and Smith 2018). This review will high-light the regulatory framework of dietary supplements, primarily focusing on the regulatory landscape in the U.S. but many similar issue exist on the global stage (Dwyer, Coates, and Smith 2018). The progress, as well as some of remaining regulatory barriers, to ensuring that all dietary supplements in the marketplace are safe are described. Given the financial incentives and competing interests of the dietary supplement industry and regulatory bodies, there are quite divergent viewpoints for how to address the existing barriers to dietary supplement regulation (Dwyer, Coates, and Smith 2018).

History of the U.S. regulatory environment for dietary supplements

Food and drugs were first regulated in the U.S. with the passing of the Pure Food and Drugs Act in 1906, which was subsequently updated with the passage of the Federal Food, Drug, and Cosmetic Act (FFDCA) of 1938 (Meadows 2006; Swann 2016). The FDA was charged with enforcing these laws with a critical function of assessing the safety of new dietary ingredients under the 1958 Food Additive Amendments to the FFDCA (Swann 2016; 85th US Congress 2018). Over the next 50 years, efforts have been attempted to introduce a number of regulations governing dietary supplements, including defining nutrients of essential and significant value, introducing minimum and maximum nutrient limits to add to products based on the Recommended Dietary Allowance (RDA), defining products that contain more than 150% of the RDA as “drug supplements,” and placing limitations on health claims (Swann 2016). However, all of these proposals were met with substantial opposition from industry and consumer groups (Swann 2016). In 1994, substantial changes were made in the regulation of dietary supplements through the enactment of U.S. Dietary Supplement Health and Education Act (DSHEA).

DSHEA legally defined the term “dietary supplement” (Box 1), outlined the regulation of dietary supplements under a food model, and mandated some required assurances for new ingredients (Food and Drug Administration; Center for Food Safety and Applied Nutrition

1995; National Institutes of Health Office of Dietary Supplements 2013). The DSHEA definition of a dietary supplement is a non–tobacco-based product that is intended to supplement the diet and contains at least one of the following: vitamins, minerals, herbs/botanicals, or amino acids, or a concentrate, metabolite, constituent, extract, or combination of these ingredients that seeks to increase total intake (Food and Drug Administration; Center for Food Safety and Applied Nutrition 1995). These rules cover products that are intended for oral ingestion in the form of pills, capsules, tablets, and liquids (Food and Drug Administration; Center for Food Safety and Applied Nutrition 1995). Dietary supplements are not permitted to represent conventional foods or be intended as sole items of a meal or the diet.

DSHEA also established labeling rules and described guidelines for promotional literature, claims, and nutritional support statements. Under DSHEA, supplement labels cannot include disease prevention or treatment claims, but they can feature other claims (Food and Drug Administration; Center for Food Safety and Applied Nutrition 1995). DSHEA outlined the three categories of permissible claims that can be displayed on products: nutrient content claims, structure/function claims, and health claims. Manufacturers need to have evidence that supports their claims before marketed. More details on requirements and definitions of these claims can be found elsewhere (McNamara 1999). Furthermore, labels must describe products as dietary supplements, list all ingredients and nutritional information, display a supplement facts panel, and provide the manufacturer’s name, location, and contact information (2005).

As dietary supplements are considered as a subset of foods under the DSHEA, the regulations are largely post-market approach (Dwyer, Coates, and Smith 2018). Stated differently, manufactures of supplement products do not have document quality, safety and efficacy in the same way that pharmaceutical products do (Table 1, Box 2). Some exceptions include that manufacturers should notify FDA of products with new dietary ingredient before marketed. Under DSHEA, FDA conducts post-market site audits for manufacturers for Good Manufacturing Practice (GMP) compliance, discussed in detail below.

DSHEA gave the FDA the authority to establish regulations relating to GMP designed to ensure that preparation, packaging, and storage of dietary supplements results in safe, clean, and wholesome products (Food and Drug Administration; Center for Food Safety and Applied Nutrition 1995; US Department of Health and Human Services; Food and Drug Administration 2007). These regulations dictate that not only should quality control, batch consistency, and plant sanitation be maintained, but also that manufacturing personnel are adequately trained and that, at every step in the manufacturing process, all of these facets are properly documented. However, before 2007, GMP regulations were modeled after the food industry and therefore did not require the same standards as those used for over the counter drug products and pharmaceuticals. The current GMP (cGMP) guidelines, developed in 2007, established rules directed specifically to dietary supplements and attempted to ensure that each product contained the actual ingredient on the label at the intended purity, strength, and composition (US Department of Health and Human Services; Food and Drug Administration 2007). While this advanced the regulations to align more with pharmaceuticals in some ways, these rules are less rigorous for dietary supplements because

they allow manufacturers to set their own quality specifications (Sarma, Giancaspro, and Venema 2016). cGMP outlines verification standards requiring confirmation that appropriate procedures and control measures have been performed (LeDoux et al. 2015). Validation refers to the confirmation that these measures actually worked and are effective (LeDoux et al. 2015) and are under the purview of the product manufacturer. Thus, there is no premarket approval process that is required for dietary supplements (US Pharmacopeial Convention 2017). Compliance with and enforcement of cGMP are limited given the enormity of the industry in comparison to the FDA budget and staff for monitoring pharmaceuticals. Almost 13,000 dietary supplement facilities were registered with the FDA in 2015, yet only a fraction were inspected that year for compliance (Long 2016). Of the facilities that were inspected, 58% were cited with “observations” or violations of cGMP. Furthermore, FDA inspectors found that 19% of the cited companies failed to set specifications for identity, purity, strength, and composition of the final product, and 16% of these companies failed to verify the identity of a dietary ingredient through an appropriate test or method (Long 2016).

In 2006, Congress augmented DSHEA to require manufacturers, importers, and distributors to report serious adverse events to the FDA within 15 business days of receiving the report, similar to spontaneous reports for pharmaceutical products (Jiang 2009; 109th US Congress 2017). Any additional information on such a report received within 1 year of the initial submission must also be filed with the FDA (Jiang 2009; 109th US Congress 2017). Information required to be reported to the FDA is limited to medical information and does not include anything related to any litigation (109th US Congress 2017). Manufacturers are also required to maintain detailed records related to adverse event reports received for 6 years, regardless of severity (109th US Congress 2017). However, the Government Accountability Office suggests a need for better tracking of serious adverse events, including efforts to help consumers report these events (US Government Accountability Office 2017).

In January 2011, the Food Safety Modernization Act was signed into law and contained a number of provisions that impact dietary supplements (US Department of Health and Human Services; Food and Drug Administration 2013). This law gives the FDA mandatory recall authority, meaning it no longer has to rely on manufacturers to voluntarily remove adulterated or misbranded products from the market. Manufacturers are required to register their facilities biennially, compared with one initial registration under previous law, and to verify the safety of ingredients from foreign suppliers (US Department of Health and Human Services; Food and Drug Administration 2013). In 2016, the FDA issued guidance regarding what constitutes a new dietary ingredient and outlined mechanisms for notifying the agency of a new dietary ingredient (US Department of Health and Human Services; Food and Drug Administration; Center for Food Safety and Applied Nutrition 2016). So while the FDA has authority to regulate manufacturers of dietary supplements and to enforce the law, almost all aspects of efficacy, safety, and quality control still remain at the discretion of the manufacturer.

Resources regarding dietary supplement quality

The next sections will describe federal and nonfederal resources that are available to support efforts to ensure the quality of dietary supplements. The quality of a dietary supplement

generally refers to the purity and safety (i.e., lack of contamination, spoilage) of all ingredients and finished products. Efficacy, an equally important dimension of dietary supplements, is briefly touched on in later sections.

Federal resources

DSHEA outlined the creation of the Office of Dietary Supplements (ODS; https://ods.od.nih.gov/) at the National Institutes of Health (NIH). The NIH/ODS has also led several research initiatives to increase the scientific rigor surrounding dietary supplement research and methods. ODS together with other Federal agencies works to support research and safety of dietary supplements through a variety of programs that are germane to the quality of dietary supplements.

The National Institute of Standards and Technology (NIST) in collaboration with the ODS, through the Analytical Methods and Reference Materials Program, established the Dietary Supplement Laboratory Quality Assurance Program (Phillips, Rimmer, and Wood 2016). NIH/ODS also funds development and validation of analytical methods and reference materials and methods for select dietary supplements to provide industry, researchers, and regulators with the tools needed to verify label claims, comply with regulations, and develop quality standards (Saldanha, Betz, and Coates 2004; National Institutes of Health 2017). For manufactures this is a resource that Dpermits examining compliance with cGMP and other regulations, while for researchers these tools help accurately characterize products for use by allowing “in-house” laboratories to measure nutritional elements, contaminants, water- and fat-soluble vitamins, fatty acids, and botanical marker compounds in ingredients and finished products (Phillips, Rimmer, and Wood 2016). NIST and NIH/ODS have developed a number of assays using an array of analytical techniques to determine the quality of MVM ingredients and final products, including inductively coupled plasma (ICP)-optical emission spectrometry, ICP mass spectrometry (MS), ICP/MS isotope dilution, prompt-gamma activation analysis, instrumental neutron activation analysis, radiochemical neutron activation analysis, and X-ray fluorescence spectrometry (Turk et al. 2013). Other techniques such as DNA barcoding and next-generation sequencing-facilitated barcoding are being developed to standardize assessment of botanical dietary supplements, although it is not clear how quickly these techniques will be adopted by industry (Coutinho Moraes et al. 2015).

The publically available and searchable Dietary Supplement Ingredient Database (DSID) conducts detailed chemical analyses to estimate the actual ingredient content as purchased relative to the label declarations on the products sold in the U.S (Dwyer, Coates, and Smith 2018; National Institutes of Health; Office of Dietary Supplements 2017; Dwyer et al. 2008). DSID was developed by the Nutrient Data Laboratory of the U.S. Department of Agriculture in collaboration with NIH/ODS (National Institutes of Health; Office of Dietary Supplements 2017). DSID also provides statistical tools to convert label declarations into analytically predicted ingredient amounts to enable accurate estimation of intakes (Andrews et al. 2018). DSID reports have demonstrated the variability of some ingredients in dietary supplements from label declarations (Roseland et al. 2008). For example, MVM products tend to have notable “overages” of some ingredients compared with the label; this is salient

as many MVM products have 100% or more of the recommended daily values (Andrews et al. 2017).

In 2013, federal efforts by the NIH/ODS and the National Library of Medicine launched and released the Dietary Supplement Label Database (DSLD). DSLD represents a free, open-access database of supplement labels and product information of currently and historically marketed products since 2012. More on the functions and potential of the DSLD is described elsewhere (Dwyer, Coates, and Smith 2018).

The FDA has long worked together with the Federal Trade Commission (FTC) to regulate advertising claims relating to dietary supplements (Federal Trade Commission Bureau of Consumer Protection 2001). The FTC Advertising Law is designed to "prohibit unfair or deceptive acts or practices in commerce" (Section 5) and "prohibits false ads" (Section 12), this is inclusive, but not limited to, dietary supplements. The FTC and FDA work together, and a liaison agreement exists whereby the FDA has primary authority for labeling claims on products and the FTC has primary authority over advertising, including print, broadcast, internet, infomercials, and other direct marketing materials. The role of the FTC and advertising standards are the same with dietary supplements as with other products such as foods; promoting dietary supplements must be truthful, not misleading, and substantiated with scientific evidence. The FTC has issued guidance to the supplement industry to clarify their policies and enforcement practices related to dietary supplements (Federal Trade Commission Bureau of Consumer Protection 2001). Under the FTC act, manufacturers are responsible for the accuracy of claims that are both expressly stated, suggested, or implied by an advertisement (Federal Trade Commission Bureau of Consumer Protection 2001).FTC does not have the ability to remove products from the marketplace, only FDA can do this.

Industry and commercial resources

The work of DSID is broadly in line with that of some independent (i.e. third-party) groups such as Consumer Lab that also compare the actual analytical levels of product ingredients with the labeled levels for a wide range of product types, often referred to as third-party certification. For example, in a recent analysis of MVM, Consumer Lab found quality control problems with 46% of MVM products; the levels of vitamin A, vitamin D, folate, and/or calcium ranged from 24% to 157% of the values listed on the label. The same analysis found that many supplements exceeded the upper tolerable intake level for some ingredients (ConsumerLab.com 2017).

Several other third-party verification programs exist, and some manufacturers have adopted their standards and display their certification symbols on their packaging. For example, the U.S. Pharmacopeia Convention (USP) has continuously developed and revised science-based quality standards for medicines and has recommended applying the science-based USP National Formulary public standards to dietary supplements in order to strengthen GMP provisions (Sarma, Giancaspro, and Venema 2016). The USP framework seeks to ensure that manufacturers follow standards of consistency and quality, establish registries that promote transparency of standards for dietary supplements and promote the surveillance of quality and safety concerns (US Pharmacopeial Convention 2017). The American Herbal Products Association developed a guidance document for manufacturers seeking to market

organic dietary supplements that utilize organic botanical- or animal-based sources of vitamins, minerals, and herbs free of pesticides and other potentially dangerous chemicals, using National Organic Program guidelines (American Herbal Products Association 2018). The extent of of use of third-party certification by manufactures is largely unknown, but one study documented its use in only a minority of cases (Cancio et al. 2012). More details on third-party certification is reviewed elsewhere (Cancio et al. 2012).

The dietary supplement industry, led by the Council for Responsible Nutrition, has launched a self-regulatory initiative called the Supplement OWL® (Online Wellness Library) (2005). This registry allows manufacturers to voluntarily provide product labels as well as information on manufacturing and packaging facilities, (the latter is available only to the FDA). Companies can provide additional information, including in regards to the quality control practices that they voluntarily employ. As April of 2018, 10,000 supplement labels were listed in the OWL®, far fewer than the DSLD.

Limitations of existing regulations and resources

Despite regulatory and voluntary guidelines and public and private efforts to improve the marketplace, many challenges remain and, as a result, the of products in the marketplace can be highly variable and many safety issues have been documented with a number of products (Jiang 2009). Several issues with dietary supplements simply are not covered under the DSHEA legislation. This section will highlight some of the major issues that remain.

Because dietary supplements and their ingredients are manufactured in different countries around the world, the provenance or mislabeling of source materials can lead to safety concerns. Safety issues arise when there is accidental or deliberate inclusion of ingredients in products (such as controlled substance or analogs to prescription drugs), microbial contamination (e.g. mold, baceteria, viruses, yeast), and misbranding of branding of products. For example, Chinese star anise is reputed to have health benefits, but Japanese star anise is highly toxic and can cause death if mistaken for the Chinese version; any mislabeling of the two could be potentially lethal (Vermaak, Viljoen, and Lindstrom 2013). Incomplete labeling can also pose threats. An analysis of eight botanical products found that all contain phytoestrogens not listed in labels, suggesting botanical and multi-ingredient dietary supplements could contain unexpected ingredients that can result in unforeseen health problems (Grippo et al. 2007). Botanicals that have been used as traditional medicines in some countries and cultures (e.g. traditional Chinese medicine) and may cause unexpected effects when consumed by other populations at different doses in different forms than traditionally used (e.g., *aristolochiaceae*) (Shaw 2010). As the market for dietary supplements and raw ingredients become global, efforts to cooperate regulatory approach between countries, industries, and consumers are needed The National Academies have proposed a framework regarding the safety of dietary supplements (Institute of Medicine, National Research Council 2005).

Contamination and adulteration

Deliberate contamination or adulteration with active compounds is also of concern. Some dietary supplements have been shown to contain synthetic drugs and drug analogs, despite

not being included on the label (Sarma, Giancaspro, and Venema 2016; Cohen 2009; Hamburg 2010). A comprehensive analysis of traditional Chinese medicine found that most of the samples were contaminated or adulterated with undeclared ingredients, pharmaceutical agents and/or heavy metals (Coghlan et al. 2015). Particular categories of supplements tend to be prone to such issues and are more likely to be removed from the market, including products for sexual enhancement, body building, and weight loss (Harel et al. 2013). Safety issues have plagued high user groups like athletes and military personnel (Knapik et al. 2018; Knapik et al. 2016; Knapik et al. 2014; Austin, Farina, and Lieberman 2016). For example, athletic performance supplements have been found to contain anabolic agents and amphetamines, while weight loss supplements have been found to contain anorectic agents such as phentermine, fenfluramine, and ephedrine (Cohen, Travis, and Venhuis 2014; Maughan 2013). Furthermore, supplements that are used for promoting sexual health have been found to contain phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil and tadalafil (Cohen and Venhuis 2013). PDE-5 inhibitor analogs are not registered as drug products, have no known safety profile, and can have negative health consequences (Cohen and Venhuis 2013). In the Netherlands, 74% of sexual health supplements seized were found to contain one of these PDE-5 inhibitor analogs (Venhuis and de Kaste 2012). However, PDE-5 inhibitor analogs that have not been characterized can be synthesized and cannot be detected by regulatory agencies (Cohen and Venhuis 2013). These products are illegal as they do not meet the regulatory definition for a dietary supplement and should instead be regulated as a drug.

In an attempt to combat the issue of including ingredients that are drug- and not nutrient-based, the FDA issued a letter in 2010 noting that it is the responsibility of manufacturers, distributors, importers, and others in the supply chain to ensure that products comply with regulations and do not contain active ingredients that may cause a supplement to be misbranded, adulterated, and/or classified as an unapproved new drug (Hamburg 2010). The FDA further recommended that all manufacturers review their manufacturing and quality assurance activity, while further noting that it is critical for dietary supplement manufacturers to not only assay their final product to ensure consistency, but also to qualify suppliers and test sources of ingredients, as raw ingredients may already be contaminated (Hamburg 2010).

Adverse event reporting

Before FDA can remove a dietary supplement from the marketplace, safety issues must be identified – this can happen through adverse event reporting, product sampling, new information in the scientific literature, and other types of supporting documentation (Brown 2017). Serious adverse events are required to be reported to the FDA, but other adverse events can be reported voluntarily at the discretion of the manufacturer (Timbo et al. 2018). It is not until a product safety is questioned or verified that it can removed from the market.

During a period from 2004 to 2012 as many as 237 products were banned from the marketplace (Harel et al. 2013). A frequently cited example is the use of ephedra-containing dietary supplements that were marketed for weight loss (Seamon and Clauson 2005; US Department of Health and Human Services; Food and Drug Administration 2004). These

products contained sympathomimetic ephedrine alkaloids that were associated with a number of cases of stroke, cardiac arrhythmia, and death, which ultimately led the FDA to ban the marketing of ephedra as a dietary supplement (US Department 2004). Incidents such as this led to calls for stricter regulation and scientific research of dietary supplements (Jiang 2009); but have not addressed the root cause and as a result safety issues remain today. A more recent example of safety concern include kratom (*mitragyna speciose*), a botanical is indigenous to Southeast Asia; it is currently being used as a dietary supplement for pain management. Kratom use has been associated with adverse medical outcomes and deaths (Anwar, Law, and Schier 2016; Warner, Kaufman, and Grundmann 2016), and Kratom products have been found to be adulterated with potentially addictive plant alkaloids (Lydecker et al. 2016). In 2016, FDA issued an import alert and proposed to classify Kratom as a Schedule I drug, but soon withdrew the proposal in response to multiple objections. Nonetheless, FDA has issued a public health advisory and statement regarding its opioid properties and a documented salmonellosis outbreak (National Center for Complementary and Integrative Health 2018).

Stability and shelf life issues

The stability and shelf life of a product are affected by a number of environmental factors, including temperature and exposure to oxygen, moisture, and ultraviolet light, all of which can influence product quality across all aspects of the supply chain: manufacturing, storage, and distribution (LeDoux et al. 2015). The primary concerns in this arena are that the product contains the amount of ingredient listed on the label throughout its shelf life and that products are safe and palatable to the consumer (LeDoux et al. 2015). To address sublimation or degradation, some manufacturers deliberately compensate for the potential loss of labile ingredients by including more than the amount stated on the label in order to ensure that the labeled amount is valid at the end of the product's shelf life (LeDoux et al. 2015). This is a common practice and complies with the FDA regulation that a product must contain the labeled ingredient amounts when its expiry date is reached (Andrews et al. 2017). No regulation exists regarding how much above the labeled amount an ingredient can deviate (LeDoux et al. 2015). Despite the efforts of DSID to document such overages for MVM products, the amounts of overage within specific product brands are generally unknown or publically unavailable. In an analysis of MVM products, the difference between labeled and measured amounts ranged from −6.5% to 8.6%, −3.5% to 21%, 7.1% to 29.3%, −0.5% to 16.4%, and 1.9% to 8.1% for thiamin, vitamin B_6, calcium, iron, and zinc, respectively (LeDoux et al. 2015; Andrews et al. 2017). In that analysis, dose overages for most ingredients were observed in the products that were evaluated, reaching as high as 25% greater for selenium and iodine. Despite the best intentions of manufacturers to increase content to match the label, such overages may lead some consumers to exceed recommended intake levels. Importantly, there is a high degree of variability between individual MVM products that are available in the U.S (Andrews et al. 2017; ConsumerLab.com 2017). The stability and shelf life of MVM are quite complex, as they contain many active ingredients, some of which are unstable (LeDoux et al. 2015). In addition, the rate of loss of activity varies from nutrient to nutrient; therefore, a test of MVM quality would require assessment of the most labile ingredients. Some manufacturers, however, assay all ingredients continuously under a range of conditions, periodically testing at least one sample from each

batch produced to ensure quality is maintained over the shelf life of each product made available for sale.

An analysis of omega-3 fatty acid supplements found that only 42% contained 90% to 110% of the declared amount of EPA (eicosapentaenoic acid). The same study showed that almost half of these supplements were in the early stages of rancidity and that the majority had peroxide levels higher than recommended by the Global Organization for omega-3 fatty acid supplements containing EPA and DHA (docosahexaenoic acid) (Opperman and Benade 2013). The presence of such contaminants may affect biological activity. For instance, saturated fats and oxidized lipids, including peroxides and secondary oxidation products, were found to be present in a fish oil supplements at levels that may actually counter the beneficial health effects of the omega-3 fatty acids (Mason and Sherratt 2017). In addition, a Dutch analysis of vitamin D supplements showed that vitamin D contents ranged from 8% to 177% of the labeled value; supplements generally contained similar to or higher vitamin D concentrations than the declared value (Verkaik-Kloosterman, Seves, and Ocke 2017).

While it may be possible to model and predict the kinetics of ingredient stability and the biological effects of the breakdown of nutrients over time, such factors are much more difficult to determine with botanicals (Saldanha et al. 2015). In many cases, the bioactive compound has not been identified, let alone all of the other compounds that may be present in the supplement (Saldanha et al. 2015). Furthermore, the stability of these compounds, their identity, and the potential activity and/or safety of any breakdown products have rarely been studied. The DSID botanical initiative may contribute to identifying variations in botanical ingredient amounts (Andrews et al. 2018). One analysis of green tea products found that 11 of 23 green tea leaf products and 8 of 14 green tea-containing tablets had total catechin levels that fell within the target range set by DSID (Saldanha et al. 2015). The American Herbal Products Association provides information for manufacturers to meet shelf life regulations (Association AHP 2011). It is more challenging to study shelf life and stability of herbal and botanical products and variations in ingredient amounts because many of these products do not list the amount of all ingredients (Saldanha, Dwyer, and Betz 2016). Manufacturers have flexibility on labeling the ingredients without official daily values. However, given the multi-ingredient nature and diversity of composition, the stability and shelf life of herbals and botanicals need further investigation.

Bioavailability

Product bioavailability or the ability of the body to absorb ingredients from different formulations is a critical issue that varies with different products and can depend on the form of the nutrient, the components/ingredients in the product, matrix, and properties of the product such as dissolution and disintegration (Yetley 2007). For example, it has been shown that using calcium salts as fillers for calcium supplements and MVM in a tablet or capsule can prevent dissolution and delay disintegration by as long as 4 to 6 hours, which can potentially reduce the bioavailability of these ingredients (Srinivasan 2001). For mineral supplements, the particular salt form of the ingredient can affect the bioavailability; calcium carbonate and calcium citrate, for example, have different absorption kinetics (Harvey, Zobitz, and Pak 1988; Heller et al. 1999). The bioavailability of individual micronutrients is

further complicated for MVM by the fact that they contain vitamins and minerals that are preferentially absorbed in different parts of the alimentary tract (Shankar, Boylan, and Sriram 2010) and have different solubility (e.g., fat soluble versus water soluble) (Srinivasan 2001). There is also the potential for interaction between different ingredients from the same product. For example, calcium can affect the body's ability to absorb iron (Benkhedda, L'abbe, and Cockell 2010).

In response to concerns regarding the bioavailability of vitamins and minerals, USP has developed dissolution standards (Srinivasan 2001). Riboflavin (i.e., vitamin B_2) has been set as the primary index vitamin as it is the least soluble of the water-soluble vitamins, based on the assumption that if sufficient time is available for riboflavin dissolution, then dissolution of other vitamins will likely be sufficient as well. Dissolution standards for folic acid have also been developed due to its importance for preventing neural tube defects and other conditions (Srinivasan 2001). Similar to pharmaceutical agents, there are other considerations for determining the bioavailability of dietary supplements, including age, sex, and race/ethnicity that would require clinical evaluations (Wood and Tamura 2001). For example, the absorption of vitamin B_{12} has been shown to decrease with age in individuals with compromised gastric acid secretion (Otten, Hellwig, and Meyers 2006). However, it should be noted that while dissolution and dissolvability of a product does not actually reflect the ability of the body to absorb the ingredients/nutrients within a product, but it stands to reason that there is a higher likelihood of absorption, if present, in products that have good dissolution and dissolvability. Nevertheless, the DSHEA legislation does not cover issues germane to bioavailability – i.e. whether the ingredients within the product can actually be absorbed by the body.

Excessive intake and interactions

Many safety issues are also related to high dose products and drug interactions. Intakes of some nutrients from dietary supplements can lead to excessive intakes above the Tolerable Upper Intake Levels (UL) that are associated with adverse health outcomes (Bailey et al. 2011; Bailey, R. L., V. L. Fulgoni, D. R. Keast, and J. T. Dwyer 2012; Bailey, R. L., V. L. Fulgoni, D. R. Keast, C. V. Lentino, and J. T. Dwyer 2012). In the U.S., supplement formulations should be considered within the context of fortification practices (Dwyer 2015, 102; Dwyer 2014, 103; Fulgoni 2011, 104). Interactions of some dietary supplement ingredients with other ingredients, foods and nutrients, and drugs can also cause adverse reactions (Gurley, Fifer, and Gardner 2012; Tsai et al. 2012). Those who consume multiple supplements (sometimes called stacking) or intensive amount of certain ingredients, such as athletes or military personnel, need more attention (Knapik et al. 2018; Knapik et al. 2016; Deuster and Lieberman 2016). Those who use multiple drugs (i.e. polypharmacy), especially older adults, need to be monitored for adverse outcomes (Gahche et al. 2017; Loya, Gonzalez-Stuart, and Rivera 2009; Agbabiaka et al. 2017).

Lack of regulatory definitions and nutrient profiles of types of supplements

While DSHEA defines the general category of dietary supplement, no legal or regulatory definitions exist for specific product categories like MVM, calcium supplements, and herbals and botanicals (Blumberg et al. 2018). Furthermore, the specific micronutrients and

their amounts are similarly unregulated and formulations are developed by the manufacturer, often without consideration of the nutrient gaps that have been historically identified in the U.S. diet (Blumberg et al. 2018).

Even though vitamin- and mineral-containing products are the most widely consumed products, no standard legal or regulatory statutes define what an MVM is and, as a result, definitions vary. In different NHANES analyses, various definitions of MVM have been used, including products containing ≥3 vitamins (Radimer et al. 2004), ≥3 vitamins plus ≥1 mineral (Bailey et al. 2011; Bailey et al. 2013), and ≥9 (Wallace, McBurney, and Fulgoni 2014) or ≥10 micronutrients (Kantor et al. 2016). Estimating the extent of MVM use and the rationale for using them, as well as evaluating their benefits and risks, is therefore complicated by lack of a consistent scientific or regulatory definition of MVM (Yetley 2007).

Calcium supplements are another class of dietary supplements that can vary from product to product. Not only do the amounts and forms of calcium (which influences bioavailability) contained in these supplements differ, but the co-ingredients can also vary and may include vitamin D or vitamin D and magnesium. Thus, when a consumer reports to their healthcare practitioner that he or she is using a particular type of dietary supplement, the specifics may difficult to ensure.

Herbal and botanical products are a category of products defined as nontobacco plant or plant parts that are used for their flavor, scent, or potential therapeutic properties. Herbals and botanicals can also be standalone single component products, but also can be found as part of proprietary blends with amounts and other important information that may not disclosed on the label (National Institutes of Health Office of Dietary Supplements 2018). The label should state from which part of the plant (e.g., flowers, leaves, bark, fruit, seeds, stems, and roots) the supplement is derived (National Institutes of Health Office of Dietary Supplements 2013). However, many products list herbals and botanicals as part of proprietary blends, which is permissible under U.S. law. To complicate matters even further, biological variability is known to exist in the bioactive components of natural products that is described in great detail elsewhere (Sorkin et al. 2016).

Establishing efficacy

Traditionally, compared to pharmaceuticals, the efficacy of dietary supplements has not been as rigorously evaluated for their intended effects, perhaps in part because supplements are not required to be efficacious to be available to consumers (Blumberg et al. 2018). However, as the dietary supplement market continues to expand and as manufacturers seek to differentiate themselves and make specific claims about efficacy, *in vitro* studies and randomized, controlled trials will be needed to demonstrate efficacy (Dwyer, Coates, and Smith 2018). These lines of research should be encouraged to allow for greater transparency about the effectiveness of these widely consumed products and to determine any potential health benefits. Especially considering that most consumers report to use supplements primarily for health-related reasons (Bailey et al. 2013; Bailey et al. 2013), despite the DSHEA language that these products are not intended to treat or prevent disease.

Conclusions

Regulatory bodies have broad authority to legally stipulate what constitutes a dietary supplement, health claims, and manufacturing practices for dietary supplements. The ability of regulators to successfully carry out this mission, however, is hampered by the sheer number of products and manufacturing facilities, as well as a low level of adverse event reporting. The issues that apply to dietary supplements containing vitamins and minerals, from provenance of ingredient sourcing to establishing activity and amount of ingredient per dose, become far more complex when considering botanical ingredients. There is also a lack of information on the bioactivity and safety of degradation products of various nutrients and other supplement ingredients as these are not typically assayed in stability testing; this is again potentially more complex and clinically significant for botanicals. Thus, despite major regulatory progress, a need remains for continued efforts and improved techniques to assess the quality of dietary supplements, especially with regard to purity, safety, and bioactivity. Additionally, the efficacy and safety of dietary supplements should continue to be evaluated through clinical research to determine their effects on human health outcomes, if they exist.

Acknowledgments

Medical writing support was provided by Dennis Stancavish of Peloton Advantage, LLC, and was funded by Pfizer. Special thanks to Shinyoung Jun, MPH for critical scientific and technical support of this work.

Disclosure statement

Medical writing support was provided by Dennis Stancavish of Peloton Advantage, LLC, and was funded by Pfizer. Regan Bailey did not receive funding for this manuscript. She serves as a scientific consultant to the Office of Dietary Supplements and received travel support to present her research from the Council for Responsible Nutrition. Her research is currently supported through the NIH (U01CA215834) and Purdue University.

References

Agbabiaka TB, Wider B, Watson LK, and Goodman C 2017 Concurrent use of prescription drugs and herbal medicinal products in older adults: A systematic review. Drugs & Aging 34 (12): 891–905. [PubMed: 29196903]

American Herbal Products Association 2018 Guidance on formulation and marketing of dietary supplements under tha national organic program Silver Spring, MD: American Herbal Products Association.

Andrews KW, Roseland JM, Gusev PA, Palachuvattil J, Dang PT, Savarala S, Han F, Pehrsson PR, Douglass LW, Dwyer JT, et al. 2017 Analytical ingredient content and variability of adult multivitamin/mineral products: National estimates for the dietary supplement ingredient database. The American Journal of Clinical Nutrition 105 (2):526–39. [PubMed: 27974309]

Andrews KW, Gusev PA, McNeal M, Savarala S, Dang PTV, Oh L, Atkinson R, Pehrsson PR, Dwyer JT, Saldanha LG, et al. 2018 Dietary supplement ingredient database (DSID) and the application of analytically based estimates of ingredient amount to intake calculations. The Journal of Nutrition 148 (8S):1413S–21S. [PubMed: 31505677]

Anwar M, Law R, and Schier J 2016 Notes from the field: Kratom (mitragyna speciosa) exposures reported to poison Centers-United States, 2010–2015. Morbidity and Mortality Weekly Report 65 (29): 748–9. [PubMed: 27466822]

Association AHP 2011 Shelf life dating of botanical supplement ingredients and products Silver Spring, MD: AHPA.

Austin KG, Farina EK, and Lieberman HR 2016 Self-reported side-effects associated with use of dietary supplements in an armed forces population. Drug Testing and Analysis 8 (3–4):287–95. [PubMed: 26526399]

Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, and Picciano MF 2011 Dietary supplement use in the United States, 2003–2006. The Journal of Nutrition 141 (2):261–6. [PubMed: 21178089]

Bailey RL, Gahche JJ, Miller PE, Thomas PR, and Dwyer JT 2013 Why US adults use dietary supplements. JAMA Internal Medicine 173 (5):355–61. [PubMed: 23381623]

Bailey RL, Gahche JJ, Thomas PR, and Dwyer JT 2013 Why US children use dietary supplements. Pediatric Research 74 (6): 737–41. [PubMed: 24002333]

Bailey RL, Fulgoni VL, Keast DR, and Dwyer JT 2011 Dietary supplement use is associated with higher intakes of minerals from food sources. The American Journal of Clinical Nutrition 94 (5): 1376–81. [PubMed: 21955646]

Bailey RL, Fulgoni VL, Keast DR, and Dwyer JT 2012 Examination of vitamin intakes among US adults by dietary supplement use. Journal of the Academy of Nutrition and Dietetics 112 (5): 657–63.e4. [PubMed: 22709770]

Bailey RL, Fulgoni VL, Keast DR, Lentino CV, and Dwyer JT 2012 Do dietary supplements improve micronutrient sufficiency in children and adolescents? The Journal of Pediatrics 161 (5):837–42. [PubMed: 22717218]

Benkhedda K, L'abbe MR, and Cockell KA 2010 Effect of calcium on iron absorption in women with marginal iron status. The British Journal of Nutrition 103 (5):742–8. [PubMed: 19860985]

Blumberg JB, Bailey RL, Sesso HD, and Ulrich CM 2018 The evolving role of multivitamin/multimineral supplement use among adults in the age of personalized nutrition. Nutrients 10 (2): 248 DOI: 10.3390/nu10020

Brown AC 2017 An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. Food and Chemical Toxicology 107:449–71. [PubMed: 27818322]

Cancio A, Eliason MJ, Mercer J, Tran T, Deuster PA, and Stephens MB 2012 Third-party certification of dietary supplements: Prevalence and concerns. Military Medicine 177 (12):1460–3. [PubMed: 23397689]

Coghlan ML, Maker G, Crighton E, Haile J, Murray DC, White NE, Byard RW, Bellgard MI, Mullaney I, Trengove R, et al. 2015 Combined DNA, toxicological and heavy metal analyses provides an auditing toolkit to improve pharmacovigilance of traditional Chinese medicine (TCM). Scientific Reports 5 (1):17475. [PubMed: 26658160]

Cohen PA 2009 American roulette-contaminated dietary supplements. The New England Journal of Medicine 361 (16):1523–5. [PubMed: 19812394]

Cohen PA 2012 Assessing supplement safety-the FDA's controversial proposal. The New England Journal of Medicine 366 (5):389–91. [PubMed: 22276780]

Cohen PA, and Venhuis BJ 2013 Adulterated sexual enhancement supplements: More than mojo. JAMA Internal Medicine 173 (13): 1169–70. [PubMed: 23699734]

Cohen PA, Travis JC, and Venhuis BJ 2014 A methamphetamine analog (N,alpha-diethyl-phenylethylamine) identified in a mainstream dietary supplement. Drug Testing and Analysis 6 (7–8):805–7. [PubMed: 24124092]

ConsumerLab.com. 2017 Product review: Multivitamin and multimineral supplements review Accessed November 13, 2017. https://www.consumerlab.com/reviews/multivitamin_review_comparisons/multivitamins/?j=359255&sfmc_sub=4627281&l=529_HTML&u=4845606&mid=7276525&jb=28.

Coutinho Moraes DF, Still DW, Lum MR, and Hirsch AM 2015 DNA-based authentication of botanicals and plant-derived dietary supplements: Where have we been and where are we going? Planta Medica 81 (09):687–95. [PubMed: 25856442]

Cowan AE, Jun S, Gahche JJ, Tooze JA, Dwyer JT, Eicher-Miller HA, Bhadra A, Guenther PM, Potischman N, and Dodd KW 2018 Dietary supplement use differs by socioeconomic and Health-Related characteristics among U.S. Adults, NHANES 2011(−)2014. Nutrients 10 (8):1114.

Deuster PA, and Lieberman HR 2016 Protecting military personnel from high risk dietary supplements. Drug Testing and Analysis 8 (3–4):431–3. [PubMed: 26472157]

Dwyer JT, Picciano MF, Betz JM, Fisher KD, Saldanha LG, Yetley EA, Coates PM, Milner JA, Whitted J, Burt V, et al. 2008 Progress in developing analytical and label-based dietary supplement

databases at the NIH office of dietary supplements. Journal of Food Composition and Analysis 21 :S83–S93. [PubMed: 25346570]

Dwyer JT, Wiemer K, Dary O, Keen CL, King JC, Miller KB, Philbert MA, Tarasuk V, Taylor CL, Gaine PC, Jarvis AB, and Bailey RL 2015 Fortification and health: Opportunities and challenges. Advances in Nutrition 6:124–31. [PubMed: 25593151]

Dwyer JT, Bailey RL, Britten P, Carriquiry A, Edge MS, Miller D, Moshfegh A, Murphy MM, and Woteki C 2014 Fortification: New findings and implications. Nutrition Reviews 72: 127–41. [PubMed: 24447229]

Dwyer JT, Coates PM, and Smith MJ 2018 Dietary supplements: Regulatory challenges and research resources. Nutrients 10 (1):41.

Dwyer JT, Bailen RA, Saldanha LG, Gahche JJ, Costello RB, Betz JM, Davis CD, Bailey RL, Potischman N, Ershow AG, et al. 2018 The dietary supplement label database: Recent developments and applications. The Journal of Nutrition 148 (8S):1428S–35S. [PubMed: 31249427]

Federal Trade Commission Bureau of Consumer Protection. 2001 Dietary supplements: An advertising guide for industry Accessed January 18, 2018. https://www.ftc.gov/system/files/documents/plain-language/bus09-dietary-supplements-advertising-guide-industry.pdf.

Food and Drug Administration; Center for Food Safety and Applied Nutrition. 1995 Dietary supplement health and education act of 1994 Accessed May 9, 2018. https://health.gov/dietsupp/ch1.htm.

Fulgoni VL, Keast DR, Bailey RL, and Dwyer J 2011 Foods, fortificants, and supplements – Where do Americans get their nutrients? Journal of Nutrition 141:1847–54. [PubMed: 21865568]

Gahche JJ, Bailey RL, Potischman N, and Dwyer JT 2017 Dietary supplement use was very high among older adults in the United States in 2011–2014. The Journal of Nutrition 147 (10):1968–76. [PubMed: 28855421]

Gahche J, Bailey R, Burt V, Hughes J, Yetley E, Dwyer J, Picciano MF, McDowell M, and Sempos C 2011 Dietary supplement use among U.S. adults has increased since NHANES III (1988–1994). NCHS Data Brief:1–8.

Grippo AA, Capps K, Rougeau B, and Gurley BJ 2007 Analysis of flavonoid phytoestrogens in botanical and ephedra-containing dietary supplements. Annals of Pharmacotherapy 41 (9):1375–82. [PubMed: 17698891]

Gurley BJ, Fifer EK, and Gardner Z 2012 Pharmacokinetic herbdrug interactions (part 2): Drug interactions involving popular botanical dietary supplements and their clinical relevance. Planta Medica 78 (13):1490–514. [PubMed: 22565299]

Hamburg M 2010 Letter to manufacturers of dietary supplements Accessed November 28, 2017. https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/medication-healthfraud/ucm236985.pdf.

Harel Z, Harel S, Wald R, Mamdani M, and Bell CM 2013 The frequency and characteristics of dietary supplement recalls in the United States. JAMA Internal Medicine 173 (10):926–8.

Harvey JA, Zobitz MM, and Pak CY 1988 Dose dependency of calcium absorption: A comparison of calcium carbonate and calcium citrate. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research 3 (3):253–8.

Heller HJ, Stewart A, Haynes S, and Pak CY 1999 Pharmacokinetics of calcium absorption from two commercial calcium supplements. Journal of Clinical Pharmacology 39 (11):1151–4. [PubMed: 10579145]

Institute of Medicine, National Research Council. 2005 Dietary supplements: A framework for evaluating safety Washington, DC: The National Academies Press.

The organization is the Food and Drug Administration. 2005 Dietary supplement labeling guide Accessed March 21, 2018; July 19, 2018. https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/ucm070519.htm.

Jiang T 2009 The new law: Public law 109–462 for dietary supplements. European Journal of Clinical Nutrition 63 (2):300 [PubMed: 17851457]

Jun S, Cowan AE, Tooze JA, Gahche JJ, Dwyer JT, Eicher-Miller HA, Bhadra A, Guenther PM, Potischman N, and Dodd JW 2018 Dietary supplement use among U.S. Children by family

income, food security level, and nutrition assistance program participation status in 2011–2014. Nutrients 10 (9):1212.

Kantor ED, Rehm CD, Du M, White E, and Giovannucci EL 2016 Trends in dietary supplement use among US adults from 1999–2012. JAMA 316 (14):1464–74. [PubMed: 27727382]

Knapik JJ, Austin KG, Farina EK, and Lieberman HR 2018 Dietary supplement use in a large, representative sample of the US armed forces. Journal of the Academy of Nutrition and Dietetics 118 (8):1370–88. [PubMed: 29907343]

Knapik JJ, Steelman RA, Hoedebecke SS, Farina EK, Austin KG, and Lieberman HR 2014 A systematic review and Meta-analysis on the prevalence of dietary supplement use by military personnel. BMC Complementary and Alternative Medicine 14 (1):143. [PubMed: 24884570]

Knapik JJ, Steelman RA, Hoedebecke SS, Austin KG, Farina EK, and Lieberman HR 2016 Prevalence of dietary supplement use by athletes: Systematic review and meta-analysis. Sports Medicine 46 (1):103–23. [PubMed: 26442916]

LeDoux MA, Appelhans KR, Braun LA, Dziedziczak D, Jennings S, Liu L, Osiecki H, Wyszumiala E, and Griffiths JC 2015 A quality dietary supplement: Before you start and after it's marketed–a conference report. European Journal of Nutrition 54 (S1):1–8. Suppl [PubMed: 25296886]

Long J 2016 FDA still finds 'basic' GMP violations in supplement industry Accessed November 16, 2017. https://www.naturalproductsinsider.com/blogs/insider-law/2016/03/fda-still-finds-basic-gmp-violations-in-supplemen.aspx.

Loya AM, Gonzalez-Stuart A, and Rivera JO 2009 Prevalence of polypharmacy, polyherbacy, nutritional supplement use and potential product interactions among older adults living on the United States-Mexico border: A descriptive, questionnaire-based study. Drugs Aging 26 (5):423–36. [PubMed: 19552494]

Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, and Boyer EW 2016 Suspected adulteration of commercial kratom products with 7-Hydroxymitragynine. Journal of Medical Toxicology : Official Journal of the American College of Medical Toxicology 12 (4):341–9. [PubMed: 27752985]

Mason RP, and Sherratt SC 2017 Omega-3 fatty acid fish oil dietary supplements contain saturated fats and oxidized lipids that may interfere with their intended biological benefits. Biochemical and Biophysical Research Communications 483 (1):425–9. [PubMed: 28011269]

Maughan RJ 2013 Quality assurance issues in the use of dietary supplements, with special reference to protein supplements. The Journal of Nutrition 143 (11):1843s–7s. [PubMed: 24027186]

McNamara SH 1999 Structure/function claims in dietary supplement labeling: Not all of these claims need to be submitted to FDA and accompanied in labeling by the DSHEA disclaimer. Food and Drug Law Journal 54:35–42. [PubMed: 11758558]

Meadows M 2006 Promoting safe and effective drugs for 100 years Accessed January 18, 2018. https://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/.

National Center for Complementary and Integrative Health. 2018 In the News: Kratom (Mitragyna speciosa) CitedAugust 28, 2018. https://nccih.nih.gov/news/kratom.

National Institutes of Health. 2017 Dietary supplement Analytical Methods and Reference Materials Program (AMRM) Accessed November 20, 2017. https://ods.od.nih.gov/Research/amrmprogram-website.aspx.

National Institutes of Health Office of Dietary Supplements. 2013 Dietary supplement health and education act of 1994 National Institutes of Health Office of Dietary Supplements http://ods.od.nih.gov/About/DSHEA_Wording.aspx#sec5.

National Institutes of Health Office of Dietary Supplements. 2018 Botanical dietary supplements Accessed June 24, 2011; July 19, 2011. National Institutes of Health Office of Dietary Supplements web page https://ods.od.nih.gov/factsheets/BotanicalBackground-HealthProfessional/.

National Institutes of Health; Office of Dietary Supplements. 2017 Dietary supplement ingredient database Accessed November 16, 2017. https://www.dietarysupplementdatabase.usda.nih.gov/.

Opperman M, and Benade S 2013 Analysis of the omega-3 fatty acid content of South african fish oil supplements: A follow-up study. Cardiovascular Journal of Africa 24 (8):297–302. [PubMed: 24240381]

Otten JJ, Hellwig JP, and Meyers LD 2006 Dietary reference intakes: the essential guide to nutrient requirements Washington, DC: The National Academies Press.

Phillips MM, Rimmer CA, and Wood LJ 2016 Dietary supplement laboratory quality assurance program: Exercise L final report. NIST IR 8154 Accessed November 16, 2017. http://nvlpubs.nist.gov/nistpubs/ir/2016/NIST.IR.8154.pdf.

Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, and Picciano MF 2004 Dietary supplement use by US adults: Data from the national health and nutrition examination survey, 1999–2000. American Journal of Epidemiology 160 (4):339–49. [PubMed: 15286019]

Roseland JM, Holden JM, Andrews KW, Zhao C, Schweitzer A, Harnly J, Wolf WR, Perry CR, Dwyer JT, Picciano MF, et al. 2008 Dietary supplement ingredient database (DSID): Preliminary USDA studies on the composition of adult multivitamin/mineral supplements. Journal of Food Composition and Analysis 21:S69–s77. [PubMed: 24307755]

Saldanha LG, Betz JM, and Coates PM 2004 Development of the analytical methods and reference materials program for dietary supplements at the national institutes of health. Journal of AOAC International 87:162–5. [PubMed: 15084100]

Saldanha LG, Dwyer JT, and Betz JM 2016 Culinary spice plants in dietary supplement products and tested in clinical trials. Advances in Nutrition (Bethesda, Md.) 7 (2):343–8.

Saldanha L, Dwyer J, Andrews K, Betz J, Harnly J, Pehrsson P, Rimmer C, and Savarala S 2015 Feasibility of including green tea products for an analytically verified dietary supplement database. Journal of Food Science 80 (4):H883–8. [PubMed: 25817236]

Sarma N, Giancaspro G, and Venema J 2016 Dietary supplements quality analysis tools from the United States pharmacopeia. Drug Testing and Analysis 8 (3–4):418–23. [PubMed: 26857794]

Seamon MJ, and Clauson KA 2005 Ephedra: Yesterday, DSHEA, and tomorrow-a ten year perspective on the Dietary Supplement Health and Education Act of 1994. Journal of Herbal Pharmacotherapy 5 (3):67–86. [PubMed: 16520299]

Shankar P, Boylan M, and Sriram K 2010 Micronutrient deficiencies after bariatric surgery. Nutrition (Burbank, Los Angeles County, Calif.) 26 (11–12):1031–7.

Shaw D 2010 Toxicological risks of Chinese herbs. Planta Medica 76 (17):2012–8. [PubMed: 21077025]

Sorkin BC, Kuszak AJ, Williamson JS, Hopp DC, and Betz JM 2016 The challenge of reproducibility and accuracy in nutrition research: Resources and pitfalls. Advances in Nutrition (Bethesda, Md.) 7 (2):383–9.

Srinivasan VS 2001 Bioavailability of nutrients: A practical approach to in vitro demonstration of the availability of nutrients in multivitamin-mineral combination products. The Journal of Nutrition 131 (4):1349S–50S. [PubMed: 11285352]

Supplement OWL. 2018 What is the supplement OWL? Accessed January 18, 2018. http://www.supplementowl.org/what.html.

Swann JP 2016 The history of efforts to regulate dietary supple- ments in the USA. Drug Testing and Analysis 8 (3–4):271–82. [PubMed: 26593452]

109th US Congress. 2017 Public Law 109–462. Dietary Supplements 2006 December 22. Accessed November 28, 2006. https://www.congress.gov/109/plaws/publ462/PLAW-109publ462.pdf.

85th US Congress. 2018 Public law 85–929: To protect the public health by amending the Federal Food, Drug, and Cosmetic Act to prohibit the use in food of additives which have not been adequately tested to establish their safety Accessed January 18, 1958. https://www.gpo.gov/fdsys/pkg/STATUTE-72/pdf/STATUTE-72-Pg1784.pdf.

Timbo BB, Chirtel SJ, Ihrie J, Oladipo T, Velez-Suarez L, Brewer V, and Mozersky R 2018 Dietary supplement adverse event report data from the FDA center for food safety and applied nutrition adverse event reporting system (CAERS), 2004–2013. Annals of Pharmacotherapy 52 (5):431–8. [PubMed: 29171279]

Tsai HH, Lin HW, Simon Pickard A., Tsai HY, and Mahady GB 2012 Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: A systematic literature review. International Journal of Clinical Practice 66 (11):1056–78. [PubMed: 23067030]

Turk GC, Sharpless KE, Cleveland D, Jongsma C, Mackey EA, Marlow F, Oflaz R, Paul RL, Sieber JR, and Thompson RQ 2013 Certification of elements in and use of standard reference material 3280 multivitamin/multielement tablets. Journal of Aoac International 96 (6):1281–7. [PubMed: 24645505]

US Department of Health and Human Services; Food and Drug Administration. 2004 Final rule declaring dietary supplements containing ephedrine alkaloids adulterated because they present an unreasonable risk. Final rule. Federal Register 69:6787–854. [PubMed: 14968803]

US Department of Health and Human Services; Food and Drug Administration. 2007 Current good manufacturing practice in manufacturing, packaging, labeling, or holding operations for dietary supplements. Final Rule. Federal Register 72:34751–958. [PubMed: 17674484]

US Department of Health and Human Services; Food and Drug Administration. 2013 Ensuring a safe food supply: a report to congress under the FDA food safety modernization act section. 110 (a)(1) Washington, DC: Department of Health and Human Services; U.S. Food and Drug Administration.

US Department of Health and Human Services; Food and Drug Administration; Center for Food Safety and Applied Nutrition. 2016 Dietary supplements: New dietary ingredient notifications and related issues: Guidance for industry Accessed January 18, 2018. https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf.

US Government Accountability Office. 2017 Dietary supplements: FDA may have opportunities to expand its use of reported health problems to oversee products Accessed November 16, 2013. https://www.gao.gov/assets/660/653113.pdf.

US Pharmacopeial Convention. 2017 Ensuring the quality of dietary supplements Accessed November 20, 2016. https://www.usp.org/sites/default/files/usp/document/about/public-policy/public-policy-dietary-supplements.pdf.

Venhuis BJ, and de Kaste D 2012 Towards a decade of detecting new analogues of sildenafil, tadalafil and vardenafil in food supplements: A history, analytical aspects and health risks. Journal of Pharmaceutical and Biomedical Analysis 69:196–208. [PubMed: 22464558]

Verkaik-Kloosterman J, Seves SM, and Ocke MC 2017 Vitamin D concentrations in fortified foods and dietary supplements intended for infants: Implications for vitamin D intake. Food Chemistry 221:629–35. [PubMed: 27979251]

Vermaak I, Viljoen A, and Lindstrom SW 2013 Hyperspectral imaging in the quality control of herbal medicines - the case of neurotoxic Japanese star anise. Journal of Pharmaceutical and Biomedical Analysis 75:207–13. [PubMed: 23277152]

Wallace TC 2015 Twenty years of the dietary supplement health and education Act-How Should Dietary Supplements Be Regulated? The Journal of Nutrition 145 (8):1683–6. [PubMed: 26063064]

Wallace TC, McBurney M, and Fulgoni VLI 2014 Multivitamin/mineral supplement contribution to micronutrient intakes in the United States, 2007–2010. The Journal of the American College of Nutrition 33 (2):94–102. [PubMed: 24724766]

Warner ML, Kaufman NC, and Grundmann O 2016 The pharmacology and toxicology of kratom: From traditional herb to drug of abuse. International Journal of Legal Medicine 130 (1): 127–38. [PubMed: 26511390]

Wood RJ, and Tamura T 2001 Methodological issues in assessing bioavailability of nutrients and other bioactive substances in dietary supplements: Summary of workshop discussion. The Journal of Nutrition 131 (4):1396s–8s. [PubMed: 11285362]

Yetley EA 2007 Multivitamin and multimineral dietary supplements: Definitions, characterization, bioavailability, and drug interactions. The American Journal of Clinical Nutrition 85 (1):269S–76S. [PubMed: 17209208]

Zion Market Research. 2017 Global dietary supplements market will reach USD 220.3 billion in 2022: Zion Market Research Accessed November 16, 2017. https://globenewswire.com/news-release/2017/01/11/905073/0/en/Global-Dietary-Supplements-Market-will-reach-USD-220-3-Billion-in-2022-Zion-Market-Research.html.

Box 1.

The major tenets of the Dietary Supplement Health and Education Act of 1994

- Defined the term dietary supplement
  - Intended only for oral ingestion
  - Can't be represented "for use as a conventional food or as a sole item of a meal or the diet"
- Established the FDA regulatory framework for the product category that is similar to that of foods
  - Products are not required to gain premarket approval
  - Products don't have to be proven safe or effective prior to being marketed
  - In order to be removed from the marketplace, the burden of proof that a product is related to a "significant or unreasonable risk of illness or injury" must be demonstrated by the FDA
  - Requires facility registration and renewal
  - New dietary ingredient procedures developed after October 15, 1994
- Established labeling rules for the product category, including that dietary supplements cannot make disease prevention or treatment claims
- Outlined good manufacturing practices to be upheld
- Formal process for adverse event reporting procedures

Box 2.

The Food and Drug Administration approval process for pharmaceuticals1

- The FDA's definition of a drug
  - A product intended for use in diagnosing, curing/mitigating, treating, or preventing a disease and that is intended to affect the structure or function of the body
- The FDA's drug approval process involves
  - Manufacturer develops a new drug compound
  - Animal testing to determine the drug's toxicity
  - Submission of an IND application to the FDA that reports initial results and a development plan for human testing
  - Clinical trials are conducted with the drug
    - Phase 1: 20–80 healthy volunteers enrolled to determine safety and pharmacokinetics
    - Phase 2: Hundreds of patients with the disease/condition are enrolled to establish the effectiveness of the drug; safety continues to be monitored
    - Phase 3: Thousands of patients are enrolled to further explore the safety and effectiveness of the drug (i.e., different subpopulations, doses, combinations)
  - The manufacturer meets with the FDA prior to submitting an NDA
  - The NDA is the formal request to approve the drug for marketing; it includes all animal/human data, pharmacokinetics and pharmacodynamics data, and information on manufacturing processes
- The FDA reviews the NDA (~60 days) and assigns a team to evaluate the research that was conducted
- That team reviews the drug's labeling and inspects the manufacturing facility
- The FDA approves the application or issues a response letter
- Postmarketing safety analyses are conducted in phase 4 trials
- 1 Abbreviations: IND, Investigational New Drug, NDA, New Drug Application

Table 1.

Comparison of the regulatory and research requirements to bring a food, dietary supplement, or prescription drug to the U.S. marketplace[1].

	Food	Dietary Supplement	Drug
Food, Drug, and Cosmetic Act Definition	√	√	√
Regulatory Oversight	FDA-CFSAN USDA (meat, poultry, and eggs)	FDA-CFSAN	FDA-CDER
Intended use to affect structure or function of the body	√ (nutrients only)	√	√
Requires pre-market approval	Some (safety)	NDI (safety)	–
NDI notification	–	Not on market pre-1994, 75 days before being introduced or delivered for introduction into interstate commerce if not present in the food supply	
Timeframe to market	Short	Short	Long
Post-market surveillance	–	√	√
Quality and Safety			
Generally Recognized as Safe (GRAS)	√	√	–
Required to establish safety with preclinical studies	Some	Some	√
GMP	√ (FSMA)	√	√
Facility registration	√	√	√
Facility Inspection	√ (GMP, FSMA)	√ (GMP)	√ (required prior to marketing)
Potential for adulteration	√	√	√
FDA recall authority	√	√	√
Adverse event reporting	–	√	√
Labeling and Claim			
Label requirements	√	√	√
Nutrient content claim	√ (Nutrition Facts)	√ (Supplement Facts)	–
Health claims	√	If Significant Scientific Agreement (SSA) is demonstrated	–
Statement of Nutritional Support (Structure function claim)	√ (nutrients only)	Notify FDA 30 days after marketing. FDA does not approve, but reviews to ensure not a disease claim.	–
Disclaimers	–	√	–
Permitted for disease claims	–	–	√
Efficacy			
Required to establish efficacy with Phase I, II, and III trial	–	–	√
Phase IV trial	–	–	√

Crit Rev Food Sci Nutr. Author manuscript; available in PMC 2020 January 01.

	Food	Dietary Supplement	Drug
Investigational New Drug (IND) Application	–	Sometimes (depends on claim/population)	After preclinical studies to begin Phase I-III research
New Drug Application (NDA)	–	–	If preclinical and Phase III studies determine safety and efficacy

[1]Abbreviations: CDER, Center for Drug Evaluation and Research; CFSAN, Center for Food Safety and Applied Nutrition; FDA, Food and Drug Administration; FSMA, Food Safety Modernization Act; GRAS, Generally Recognized As Safe; GMP, Good Manufacturing Practice; NDI, New Dietary Ingredient.