

**USP Global Public Policy Position**

# **Regulatory reform is necessary to help ensure the quality of dietary supplements**

**Policy Position**



## Issue

To protect consumers from unsafe, poor quality dietary supplement products—such as those that are contaminated, mislabeled, adulterated—and help ensure the quality and consistency of dietary supplements sold in the United States, public health, health care, patient, consumer advocacy organizations, and the U.S. Food and Drug Administration (FDA, Agency) have called for reform to the regulation of dietary supplements.<sup>1-7</sup> The current lack of a strong regulatory framework for dietary supplements has created an environment in which a given product may vary dramatically in quality across manufacturers.

An estimated 80 percent of U.S. consumers use dietary supplements, and the dietary supplement market has grown significantly since the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994—from approximately 4,000 products in 1994 to an estimated 80,000 today.<sup>1,8</sup> Because of the growing industry and gaps in the outdated law which limits the authority of the FDA, it is difficult for the Agency to effectively or efficiently monitor the market and protect public health from dietary supplement products, and products labeled as dietary supplements, that are compromised by impurities, contaminants, and misidentified, substituted, unknown, or unlawful ingredients.

The FDA has stated three strategic priorities for dietary supplements: 1) consumer safety, 2) product integrity, and 3) informed decision-making.<sup>9</sup> The advancement of a safe and transparent marketplace will require a trustworthy supply chain and increased adherence to public quality standards. To enable the FDA to prioritize inspections, enforcement, and other regulatory actions involving products that have the greatest potential to cause harm to consumers, additional policy reform should consider enhancing dietary supplement post-market surveillance, increasing visibility into the dietary supplement market with mandatory product listing, additional labeling requirements for dietary supplement products, and the utilization of a risk-based approach for adherence to public quality standards to advance dietary supplement quality.

## Position

U.S. Pharmacopeia (USP) supports new initiatives and policies that modernize and reform the dietary supplement regulatory framework, including the Dietary Supplement Health and Education Act (DSHEA), to help ensure the quality and consistency of dietary supplements.

### 1. Improving post-market surveillance

USP supports enhancing existing efforts to improve the collection of post-market dietary supplement quality and safety signals in the FDA Safety Reporting Portal (SRP) including 1) greater enforcement of already required serious adverse event reporting by manufacturers and 2) encouraging increased voluntary reporting of suspected adverse events associated with dietary supplement products by health care professionals, researchers, public health officials, and consumers.

### 2. Adherence to public quality standards

USP supports the development and utilization of a risk-based approach for adherence to public quality standards for dietary ingredients and dietary supplement products by:

- a. Requiring adherence to the relevant public quality standards published in the *USP-NF* or the *USP Dietary Supplements Compendium (DSC)* for those ingredients and products that are identified as having a higher potential for public health risk, such as: products intended for special populations; ingredients and products that are associated with potential safety issues; products identified through post-market safety signals; and products consumed by a large number of consumers that can be a potential risk to public health; and
- b. Providing incentives, such as factors that can be used for risk-based inspection prioritization by the FDA, for firms to manufacture dietary ingredients or supplements that voluntarily adhere to public quality standards.

### 3. Increasing visibility into the market

USP supports the establishment of an FDA-administered mandatory product listing regime for dietary supplement



products that at a minimum requires dietary supplement manufacturers to provide a listing of products being sold, the ingredients contained in a product, and a copy of each product label.

#### **4. Providing ingredient transparency**

USP supports additional labeling requirements that enhance transparency of ingredients, including disclosure of all the ingredients, and their amounts, in a dietary supplement product and stability study-supported expiration dates. Providing this transparency can facilitate informed conversations and decision-making by healthcare practitioners and consumers.

#### **5. Continued education about dietary supplement quality**

USP supports continued efforts to educate consumers, patients, and healthcare professionals about the use of dietary supplement products and supports efforts to increase consumer, patient, healthcare professional, and retailer awareness of resources to help patients select quality supplements.

#### **6. Exploring opportunities to increase audits**

USP encourages exploring mechanisms, including third-party audits—where audit standards are based on Current Good Manufacturing Practices, USP Quality Standards, and FDA-established criteria—and leveraging existing FDA programs in new ways to enable increased vigilance of

dietary supplement manufacturing facilities and products.

#### **7. Increasing FDA resources**

USP encourages, in the interests of public health and consumer safety, increasing FDA resources for the oversight of dietary supplements to adequately oversee the growing dietary supplement sector; appropriately administer updated or new regulations; and explore additional regulatory reforms that correspond to the risk that specific dietary ingredients or dietary supplement products may pose to consumers.

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## **Discussion**

### **Dietary supplement trends**

Since the enactment of the Dietary Supplement Health and Education Act (DSHEA) in 1994, the dietary supplement industry has grown from \$4 billion with roughly 4,000 products in 1994 to an estimated \$60 billion in the United States, and nearly \$200 billion worldwide, by 2025<sup>10,11</sup> with somewhere between 50,000 and 80,000 products, as reported by the FDA.<sup>12</sup> Recent surveys indicate that the majority of Americans consume dietary supplement products.<sup>1,8,13-19</sup> Surveys also show that there are significant misperceptions about the safety and intended use of dietary

supplements and FDA's authorities in regulating them. Research indicates that many consumers incorrectly believe that dietary supplements are approved by the government, that dietary supplements have been tested for safety and effectiveness, that the content of all dietary supplements is analyzed, and that manufacturers are required to disclose known adverse effects.<sup>20</sup>

Since 1994, the dietary supplement industry has been reshaped by a complex global supply chain, the Internet, and newly discovered ingredients of unconfirmed safety. Industry growth, increased consumer use of products marketed as dietary supplements, and newly identified health threats all underscore the importance of understanding potential concerns about these products and warrant the need to modernize dietary supplement regulations to help ensure the quality and consistency of dietary supplements.

## Current dietary supplement regulatory landscape

### United States framework

The FDA regulates the processing, manufacturing, labeling, and packaging of dietary supplements in the United States primarily through DSHEA, enacted as an amendment to the Federal Food, Drug, and Cosmetic Act (FD&C Act) in 1994.<sup>21</sup> According to DSHEA, dietary supplements are regulated as a category of food and must include at least one “dietary ingredient.” Dietary ingredients include vitamins, minerals, herbs or other botanicals, amino acids, and dietary substances used to supplement the diet.<sup>22</sup> Dietary supplements come in many forms, including tablets, capsules, powders, gummies, and liquids, and are available for purchase over-the-counter in stores throughout the United States and via the Internet.

Dietary supplement companies are responsible for ensuring that their products are safe and lawful. Dietary supplements are not subject to preapproval requirements for safety and efficacy, nor are they required to meet official public quality standards. Unlike the framework for drugs, conformance to a *United States Pharmacopeia–National Formulary* (USP–NF)<sup>23</sup> public quality standard is voluntary for all dietary

supplements. DSHEA states that a dietary supplement shall be deemed violative if it is represented (e.g., on the product's labeling) as conforming to a standard in the USP–NF but fails to so conform.<sup>24</sup>

Under DSHEA, dietary supplement manufacturers must follow current good manufacturing practice (CGMP) requirements that are intended to ensure the quality of dietary supplements. The CGMP requirements<sup>25</sup> state that manufacturers must establish specifications for identity, purity, strength, composition, and limits on contamination for each component and for each finished dietary supplement product to ensure quality.<sup>26</sup> Additionally, manufacturers are required to set limits for specifications, including contaminants that may adulterate their products—such as microbes, microbial toxins, elemental contaminants (e.g., 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.<sup>27</sup>

However, the CGMP regulations do not include language specifying the tests and methods to be used or how to determine whether those tests and methods are appropriate and scientifically valid. Manufacturers have the flexibility to determine what tests and methods they use, including analytical methods and acceptance criteria, unless the FDA learns of a problem and deems them inappropriate or scientifically invalid. Dietary supplement products manufactured from the same ingredients by different manufacturers 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 violative<sup>28</sup>; however, the FDA can generally only make such a determination after the products are on the market. Dietary supplement products on the market are not routinely tested by the FDA to determine whether product specifications are met, are appropriate for the product, or use scientifically valid methods.

The FDA has stated that its three strategic priorities for dietary supplements include consumer safety, product integrity, and informed decision-making. In a statement, the



Agency has noted that it has a duty to protect consumers from harmful products; a responsibility to ensure that dietary supplements contain the ingredients listed on the label and nothing else, and that those products are consistently manufactured according to quality standards; and a desire to foster an environment where consumers and health care professionals can make informed decisions before recommending, purchasing, or using dietary supplements.<sup>9</sup>

## Global frameworks

The World Health Organization's *Traditional Medicine Strategy 2014–2023* includes dietary supplements in a category called Traditional and Complementary Medicines (T&CM) and recognizes that definitions for this category vary significantly globally.<sup>29</sup> As an example, certain melatonin products are regulated in the United States as a dietary supplement, in Canada as a natural health product (NHP), and in Australia as a prescription medicine.<sup>30</sup> Additionally, some countries have dosage requirements for products to be defined as dietary supplements and/or drugs. For example, vitamin D3 5000 International Units (IU) is defined as a drug in the European Union (EU) and the United States regulates certain vitamin D3 products containing below 50,000 IUs as a dietary supplement and certain vitamin D3 products containing 50,000 IUs as drug.<sup>30,31</sup> In many jurisdictions, including the United States, Canada, and Australia, T&CM products are considered suitable for self-selection without the involvement of a healthcare practitioner or a prescription. In other jurisdictions, dietary supplements or T&CM are prescribed by a professional.<sup>32–35</sup> Additionally, the context of usage of a dietary supplement varies widely from country-to-country; in some countries supplement use is just limited to general health and well-being while others permit use for medicinal purposes. To date, little consensus exists from country to country on the scope, requirements, definition, or even the terminology in which dietary supplement and herbal medicines categories could be classified. Transparent science-based quality standards for the ingredients across these regulatory frameworks and definitions has increased importance given the international supply chain of the ingredients that could be used in T&CMs.<sup>36</sup>

Similar to the variety of product definitions, no consistent global approach to product regulations exists. While global regulatory frameworks often reflect national and regional priorities, most countries regulate T&CMs as a subset of existing legislation.<sup>30,31</sup> In Canada, NHPs are regulated as a subset of drugs under the Food and Drugs Act and defined under the Natural Health Product regulations. While NHPs are not drugs, the Canadian regulations place requirements on manufacturers, distributors, importers, packagers, and labelers and require that NHP manufacturers obtain a product license through pre-market approval by the Minister of Health.<sup>37,38</sup> In Australia, the majority of T&CM products are available over-the-counter and are regulated by the Australian Therapeutic Goods Administration (TGA) using a two-tiered, risk-based approach as a subset of drugs or therapeutic goods.<sup>33,39</sup> The EU regulates some T&CM products as a subset of drugs under the Traditional Herbal Medicinal Products Directive (THMPD) and others as food supplements, which are separately regulated by the European Food Supplements Directive.<sup>30,31,40–42</sup> In China, dietary supplements are regulated as “health foods” together with functional foods, and manufacturers are required to secure product approval from the China Food and Drugs Administration (CFDA).<sup>31,43</sup>

## The importance of dietary supplement product quality

Quality of dietary supplement products can be compromised by impurities and contaminants which can occur in amounts beyond levels considered safe for human use;<sup>44</sup> ingredient misidentification or substitution, often with an inferior ingredient<sup>45–49</sup>; and products purporting to be dietary supplements but containing unknown or unlawful ingredients. Documented adherence to public quality standards can help address these quality concerns and help ensure dietary supplements' consistency and quality.<sup>50,51</sup>

The most common unlawful products marketed as dietary supplements are those promoted for weight loss, sexual function, or athletic performance.<sup>45,52–57</sup> Many times, active pharmaceutical ingredients or their analogues are identified in these categories of products marketed as dietary supplements even after FDA warnings to the manufacturer.<sup>58,59</sup> The consequences of quality assurance failures can range



from no noticeable or measurable effects to significant harms, such as internal organ damage, increased risk of cancer, or death.<sup>60</sup> The drug ingredients in these products marketed as dietary supplements have the potential to cause serious adverse events related to accidental misuse, overuse, interaction with other medications or with other ingredients within the supplement, and underlying health conditions in the user.<sup>61</sup> Many of the examples of the inclusion of unlawful ingredients and adulteration, including the identification of undeclared substances in products, can be detected using appropriate analytical methods, such as those included in public standards.<sup>23,62</sup>

As noted, although quality is built into the regulatory framework for dietary supplements, it is limited in terms of specific quality requirements.<sup>63</sup> The FD&C Act names the *USP–NF* as official compendia for dietary supplements,<sup>23</sup> but meeting the requirements in any public quality standard of the *USP–NF* is voluntary for manufacturers and distributors.

Beyond oversight by the FDA and related agencies, the dietary supplement industry can, and should, play an active and influential role in addressing dietary supplement quality. The supply chain for the manufacture and distribution of dietary supplements can involve multiple parties in many countries before a finished product is obtained. Quality issues with dietary supplement products can arise at various points and it can be difficult to track the lineage of ingredients and the identities of parties involved in the production of a single product. All stakeholders along the supply chain have the duty to self-regulate through qualifying and validating their

suppliers, ensuring supply chain security, testing ingredients and finished products, identifying and removing high-risk products from product assortments, and implementing other mechanisms to assure quality. Makers of poor-quality products ignore legal obligations and the FDA lacks the resources for more frequent inspections, substantive surveillance, and enforcement of the law.<sup>64</sup>

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## A regulatory paradigm to create trust in the quality of dietary supplements

### Improving dietary supplement post-market surveillance could improve quality and safety signal detection

To identify products that are unsafe and/or contain unlawful ingredients, the FDA relies on post-market surveillance efforts including inspection of dietary supplement manufacturing sites, review of adverse event reports and consumer complaints, and screening of imported products.

Quality concerns with dietary supplement products are widespread, as demonstrated by the number of FDA Warning Letters for dietary supplements that have not met certain CGMP and other requirements.<sup>65</sup> Within the past decade, top observations stated in FDA 483 Forms—forms issued to firms at the conclusion of an inspection when an investigator(s) has observed any conditions that may constitute violations of the FD&C Act—for dietary supplement products include failure to establish



specifications and inadequate testing or testing methods to determine if those specifications have been met.<sup>66,67</sup>

Additionally, in the United States, clinical and other research studies are not required for dietary supplements, making post-market surveillance a key part of identifying quality or safety problems associated with dietary supplement products. The FD&C Act defines a dietary supplement adverse event as “any health-related event associated with the use of a dietary supplement that is adverse”<sup>24</sup> (e.g., headache, abdominal pain, allergic reaction, rash, and dizziness or lightheadedness). A serious adverse event is defined as an adverse event that “results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or requires, based on a reasonable medical

judgement, a medical or surgical intervention to prevent an outcome described above.”<sup>68</sup> The Dietary Supplement and Nonprescription Drug Consumer Protection Act (DSNDCPA)<sup>38</sup> created a mandatory reporting system for serious adverse events for nonprescription drugs and dietary supplements, and the number of serious adverse events reported by dietary supplement manufacturers has increased since its implementation.

The U.S. Government Accountability Office (GAO) estimates that, of the estimated 50,000 adverse reactions each year from dietary supplements, a small fraction is reported to the FDA. However, literature documents that concomitant use of dietary supplements and prescribed medications is common, problematic, and can result in life-threatening adverse events, hospitalizations, and fatalities.<sup>69</sup> Many products and



ingredients have been implicated in interactions and adverse events, yet investigators note underreporting, lack of case reports, and incomplete reports.<sup>69-74</sup> The lack of reporting of adverse events from all stakeholders, along with the poor quality of the information received in some of the reports, make it difficult for the FDA to find and remove dangerous supplements.<sup>75,76</sup> The GAO has called on the FDA to improve tracking of adverse events related to dietary supplements, including utilizing data from poison centers in addition to its present sources, which mainly includes industry reports.<sup>77</sup> The FDA also underscores the importance of reporting adverse reactions to dietary supplements in resources for healthcare professionals and consumers.<sup>78</sup>

**USP supports enhancing existing efforts to improve the collection of post-market dietary supplement quality and safety signals<sup>79</sup> in the FDA Safety Reporting Portal (SRP)<sup>80,81</sup> including 1) greater enforcement of already required serious adverse event reporting by manufacturers and 2) encouraging increased voluntary reporting of suspected adverse events associated with dietary supplement products by health care professionals, researchers, public health officials, and consumers.**

### **Dietary supplement quality can be enhanced using a risk-based approach**

Reform of the current regulatory framework for dietary supplements is needed to help ensure the quality and consistency of dietary supplements sold in the United States. Adherence to public quality standards, which are developed by volunteer experts in a framework based on science and strict rules against conflict of interest, can help ensure that dietary supplements are produced according to robust scientific expectations for quality and can help reduce the potential for public health risk. Public standards can help address quality concerns, such as the presence of impurities and contaminants, and ingredient misidentification or substitution. For example, adulteration can be detected using appropriate analytical methods, and public standards can help to set appropriate specifications for identity to catch the misidentification or substitution. Public standards can be used universally and consistently by dietary ingredient and supplement manufacturers, rather than using specifications set by individual manufacturers for the same ingredients

and products. Use of a common set of quality standards throughout the industry provides transparency on the quality expectations for the ingredients and/or products for manufacturers and regulators.

A risk-based approach for adherence to public quality standards for dietary ingredients and dietary supplement products would allow the FDA to prioritize inspections, enforcement, and other regulatory actions involving products that have the greatest potential to cause harm to consumers. Risk-based regulation is used by the FDA in various product areas, including recordkeeping requirements for foods designated as high-risk<sup>82</sup> and a risk-ranking model decision support tool to assist in adding foods to the Food Traceability List;<sup>83</sup> and approaches to monitoring the conduct of clinical investigations of human drug and biological products, medical devices, and combination products.<sup>84</sup> The FDA also conducts surveillance inspections for human drug manufacturing sites using a risk-based site selection model; risk factors include compliance history and inherent product risk, among others.<sup>85</sup> The Agency has also proposed the use of risk-based approaches for building oversight of laboratory developed tests<sup>86</sup> and assessing and verifying the security and quality of software used in the medical device manufacturing and quality control process.<sup>87</sup> The FDA has indicated that they are seeking to promote best practices to help manufacturers raise their product quality and comply with existing regulations and that industry should focus on producing quality and safe products for patients at every step of the manufacturing process.<sup>88</sup>

The FDA's Compliance Program Guidance Manual for dietary supplement inspections, sampling, and imports (dietary supplement CPGM) indicates that the FDA conducts risk-based surveillance inspections for dietary supplements, focusing on compliance with CGMP, products containing ingredients at risk for contamination with higher levels of toxic elements, and supplements spiked with drug ingredients or other unlawful ingredients.<sup>89</sup> The FDA already prioritizes inspections for high-risk dietary supplements, which include, but are not limited to:

- Botanical ingredients which may contain toxic elements or microbial pathogens and may present challenges with identity and strength testing;



- Bovine ingredients;
- Supplements that may contain new dietary ingredients without safety assessments; and
- Supplements with multiple dosage forms such as powder, liquid, gummy, or softgel dosage forms.

In addition to the high-risk factors for dietary supplements indicated in the FDA's dietary supplement CPGM, such as ingredients that may contain contaminants, and to promote best practices to produce quality and safe products for consumers, the FDA should consider additional factors for dietary ingredients and supplements that have a higher potential for public health risk than others, including:

- **Products intended for special populations**, for example, prenatal vitamins and vitamin D drops for infants;
- **Ingredients and products that are associated with potential safety issues**, such as products that commonly include impurities or contaminants or products that are more susceptible to economic adulteration, such as substitution of ingredients;
- **Products identified through post-market safety signals** such as FDA 483 Forms or post-market surveillance reporting; and
- **Consumer usage or number of products on the market.**  
A large majority of Americans report taking dietary supplements, and almost all of these supplement users (98 percent) reported taking vitamins and minerals.<sup>18</sup> Another survey reported the top ten most popular supplements as vitamin D, magnesium, fish oil/omega-3, Coenzyme Q10, multivitamins, probiotics, curcumin/turmeric, vitamin C, vitamin B, and calcium.<sup>90</sup> With the large number of consumers regularly exposed to these products and the limitations associated with current post-market surveillance, there follows a substantial increase in the potential risk to public health with the most utilized products.

### **Mandatory adherence to public quality standards will help ensure quality of higher-risk products**

Similar to FDA draft guidance for verifying the security and quality of software used in medical device manufacturing

and quality control,<sup>87</sup> risk-based required adherence to public quality standards can help manufacturers raise product quality, comply with existing regulations, and focus on producing quality products for consumers at every step of the manufacturing process; which are in alignment with stated FDA priorities to improve consumer safety, product integrity, and informed decision-making.<sup>9</sup>

**To help ensure the quality of those ingredients and products identified as potentially higher-risk, the FDA should be given the authority to require adherence to public quality standards. A list of higher-risk products and ingredients should be developed for required adherence and should consider factors such as products intended for special populations; ingredients and products that are associated with potential safety issues; products identified through post-market safety signals; and products consumed by a large number of consumers that can be a potential risk to public health.**

The *USP-NF* includes more than 800 dietary-supplement-related documentary standards and approximately 200 physical reference standards to verify that a product and its ingredients can pass tests indicating adherence to quality standards. USP prioritizes the development of additional dietary supplement standards based on considerations that include the extent of use, interest from a governmental body, and potential safety risk associated with use. The majority of dietary supplement standards in the *USP-NF* are for commonly used botanicals, vitamins, and minerals, accounting for approximately 70 percent of prominently marketed ingredients. The standards for botanical ingredients help ensure quality related to ingredient misidentification and substitution.<sup>91</sup> The vitamin and mineral standards are important due to the high consumer use of these products. Requiring adherence to USP standards will help ensure the quality of these ingredients and products.<sup>92</sup>

Additionally, dietary supplement products containing impurities and/or contaminants can present potential quality and safety concerns. Some contaminants of concern include heavy metals, bacteria and fungi, toxins, and pesticides.<sup>93</sup> Adherence to public quality standards can help ensure that valid testing is conducted for the presence of impurities and contaminants in dietary supplements. Further, as noted in



FDA's dietary supplement CPGM, certain dietary ingredients may contain toxic elements or microbial pathogens and present challenges with identity and strength testing, complicated by multiple dosage forms.<sup>89</sup> USP public standards include multiple dosage forms when applicable, and limits for microbial pathogens, elemental contaminants, and other known adulterants. Admission evaluations (safety evaluations based on available literature) are part of the *USP Dietary Supplement Compendium (DSC)*.

**Incentivizing voluntary adherence with public quality standards will promote quality**

A challenge associated with required adherence to public quality standards for higher-risk products is a misconception that products outside the high-risk category are exempt from quality concerns. To address this perception, an additional consideration for a risk-based approach to dietary supplement ingredient and product oversight could include regulatory incentives to increase voluntary adherence to quality standards within the dietary supplement industry for those products not deemed higher-risk.

For example, the FDA could consider adherence to public quality standards, such as *USP General Chapters <2740> Manufacturing Practices for Dietary Ingredients* and *<2750> Manufacturing Practices for Dietary Supplements*<sup>94,95</sup> or other ingredient-specific standards, as a factor in its risk-based inspection model. In the FDA's dietary supplement CPGM, it states, "A primary objective of FDA's dietary supplement inspection program is to ensure that dietary supplement products meet federal standards for quality and accurate labeling."<sup>89</sup> Further, when the FDA performs analyses on ingredient samples, the CPGM says that "[c]ompendial methods must be considered before non-compendial methods are considered."<sup>89</sup> Additionally, "[a]ll methods used whether compendial or non-compendial, must be validated through the use of recovery and reproducibility studies, use of positive and negative controls, use of Standard Reference Material, when available, or in-house quality assurance/quality control materials, etc."<sup>89</sup>

Therefore, if dietary ingredients and supplements adhere to public quality standards, use of such validated methods could assist and facilitate FDA inspection protocols and ingredient and product test methods.

**Providing incentives, such as factors that can be used for risk-based inspection prioritization by the FDA, for firms to manufacture dietary ingredients or supplements that voluntarily adhere to public quality standards could facilitate increased quality in the dietary supplement industry.**

This approach could be a more efficient use of FDA's limited resources and staff for inspections and testing of dietary ingredients and supplements, allowing the FDA more resources to focus on prioritizing enforcement and other regulatory actions on products with a potential for higher public safety risk.<sup>89,96</sup>

**Dietary supplement mandatory product listing will provide more transparency to regulators, healthcare professionals, and help inform consumers**

Under existing law, the FDA does not have the authority to require approval of dietary supplement labeling before dietary supplements are sold. Post-market oversight of dietary supplement marketing, including labeling and advertising, are shared authorities between the FDA and Federal Trade Commission (FTC). The FTC acts as the primary regulator of dietary supplement advertising and the FDA possesses primary regulatory responsibility for dietary supplement labeling.<sup>97</sup>

Under DSHEA, manufacturers and distributors of dietary supplements and dietary ingredients are prohibited from marketing products that are adulterated or misbranded and manufacturers are responsible for labeling their products to ensure that they meet all the requirements of DSHEA and FDA's implementing regulations.<sup>32</sup> The FDA can take action against any adulterated or misbranded dietary supplement once a product on the market is found to be in violation. Post-market surveillance methods such as adverse event monitoring, inspections, and Internet searches are the primary means to monitor the safety of marketed products. The FDA can only restrict the use of a product or mandate a recall once the product is being marketed.<sup>98,99</sup> Because dietary supplement manufacturers are not required to submit certain product information before marketing, the FDA has insufficient authority and resources for real-time and useful monitoring to know which dietary supplement products are on the market or any additional information about them.

The FDA noted in a 2022 draft guidance that it currently lacks information about an estimated 4,600 new supplement ingredients.<sup>100</sup> Because there are an unknown number of dietary supplement ingredients and products currently on the market, additional transparency for the FDA and the public about the type and volume of dietary supplement



products available on the U.S. market could facilitate FDA regulatory actions.<sup>12,101</sup>

**USP supports modernization of DSHEA, granting the FDA the authority to establish an FDA-administered mandatory product listing regime for dietary supplement products. This system would require dietary supplement manufacturers to provide at a minimum a listing of products being sold, the ingredients contained in the product, and a copy of each product detail.**

With mandatory product listing authority, the FDA could require dietary supplement manufacturers to provide basic information about the products being sold, including the ingredients contained in the product, a copy of the label, and information about whether the product complies with public quality standards. Requiring dietary supplement manufacturers to list all products marketed as dietary supplements with the FDA would support greater transparency in the supply chain and would provide the FDA with a comprehensive view of the products potentially on the market.<sup>6</sup>

Public health, health care, patient, and consumer advocacy organizations have long called for reform of the DSHEA framework and many have specifically called for mandatory product listing.<sup>1-3,5,102,103</sup> The concept of a mandatory product listing for dietary supplements has had bipartisan Congressional support and is supported by the FDA and 95 percent of American adults.<sup>6,104-107</sup> Some trade organizations also support the concept of mandatory product listing.<sup>108</sup> Additionally, some advocates for dietary supplement safety call for additional safeguards to be integrated in the listing system, such as quick response (QR) codes for easy identification and the ability to flag products produced by manufacturers who have received warning letters from the FDA to further boost transparency and facilitate the recall of harmful products more quickly and thoroughly.<sup>63,73</sup>

A mandatory product listing would provide additional transparency to the FDA and the public on the type and number of dietary supplement products available on the U.S. market and would help facilitate FDA actions against non-compliant products and the manufacturers and/or distributors of such products. It would provide the FDA and

industry the ability to respond more quickly to emerging safety concerns, support FDA efforts to prioritize resources and expertise, promote risk-based regulation, support consumer access to quality products, and increase the transparency and awareness of the ingredients in dietary supplements.<sup>109</sup>

### **Additional labeling requirements could facilitate dietary supplement quality**

Regulatory reform should also provide additional authority to the FDA to require that firms adhere to additional labeling requirements related to transparency of ingredients and the quality of the product. Currently, dietary supplement labeling must include: 1) the statement of identity (including the term “dietary supplement” or “supplement” and a modified and appropriately descriptive term indicating the type of dietary ingredient(s) in the product); 2) the net quantity of contents statement (amount of the dietary supplement); 3) the Supplement Facts labeling; 4) the ingredient list; and 5) the name and place of business of the manufacturer, packer, or distributor.<sup>110</sup> Additionally, the FDA requires manufacturers to list all the ingredients in a dietary supplement on the Supplement Facts panel of the product, along with the amount of each by weight, except when the ingredients are part of “proprietary blend;” proprietary ingredients are disclosed, but not their amounts.<sup>111</sup> **Manufacturers should be required to disclose all of the ingredients, and their amounts, in a dietary in a dietary supplement product. Listing out the amounts of the ingredients in a proprietary blend would improve the transparency of ingredients included in such dietary supplements, help the FDA determine if a labeled ingredient is new and/or lacks adequate safety evidence, and provide necessary information to consumers and healthcare providers.**

Additionally, there is currently no requirement for manufacturers to include expiration dates on dietary supplement products. However, if such information is placed on the label, the manufacturer must have data to support the expiration date.<sup>112</sup> **To support the quality and stability of the product, labeling requirements should include expiration dates supported by stability studies.**





### Continued education can facilitate awareness about dietary supplement quality considerations

Many people purchase and consume dietary supplement products without advice from a healthcare professional. Without engagement in risk-based conversations about dietary supplement product use with a healthcare professional, important quality factors may not be considered or understood. These risk-based conversations should include discussion about the variable quality of dietary supplements, the presence of unreputable products in the marketplace, and information on which products are commonly adulterated. As noted, surveys indicate that a majority of Americans consume dietary supplement products and have misperceptions about the safety and intended use of dietary supplement products.<sup>1,8,13-19</sup> Many people report purchasing dietary supplement products in pharmacies,<sup>113</sup> however, a minority of consumers report discussing dietary supplements with a healthcare professional<sup>114</sup> and 75 percent of people report using at least one dietary supplement without a recommendation from a physician.<sup>115</sup>

Healthcare professionals, including pharmacists and physicians, provide guidance and answer patient and consumer questions regarding medicines and dietary supplements. Consumers are inundated with options when they go to purchase dietary supplement products.

Resources are available to educate healthcare professionals and consumers about how dietary supplements are regulated in the United States, benefits, and risks of using dietary supplement products, and choosing dietary supplements with quality in mind.<sup>78,116</sup>

**USP supports continued efforts to educate consumers, patients, and healthcare professionals about the use of dietary supplement products and supports efforts to increase consumer, patient, healthcare professional, and retailer awareness of resources to help patients select quality supplements.**

### Opportunities to increase audits should be explored

Public quality standards provide valuable information to manufacturers to support building critical quality attributes into processes beginning in the early development phases of new and existing products and address common quality issues. Standards, such as *USP General Chapters <2740> Manufacturing Practices for Dietary Ingredients*, *<2750> Manufacturing Practices for Dietary Supplements*,<sup>94,95</sup> ingredient-specific standards when available,<sup>23</sup> as well as associated analytical methods provide tools to create efficiency in product development, create consistency across manufacturers, and increase transparency in quality expectations for industry and regulators.

All supplements marketed and sold in the United States must comply with the CGMP requirements in 21 CFR 111 and portions of 21 CFR 117,<sup>21,117</sup> and the top violations cited in manufacturer audit reports include failure to set proper specifications for products that are manufactured and insufficient quality control operations.<sup>118</sup> As a means to drive product quality and the production of consistent dietary supplement products, USP encourages conducting more risk-based FDA audits as outlined in the CPGM at the dietary supplement product level, however, also recognizes that the FDA currently lacks the resources to more frequently audit all listed manufacturing facilities.

Some policy proposals include: 1) consideration of authorizing third-party CGMP dietary supplement auditors to better enforce regulations, more frequently audit, and ease the burden on the FDA;<sup>2</sup> 2) leveraging the existing Voluntary Qualified Importer Program (VQIP) along with remote regulatory assessments;<sup>119,120</sup> or 3) some combination of these proposals. Questions remain about the goals and logistics of some proposals since varying quality standards can exist<sup>23,121-123</sup> with current dietary supplement third-party audits that may differ from—sometimes with requirements below—FDA CGMP requirements.<sup>25</sup> Some programs evaluate only a manufacturing facility to ensure the facility has the CGMP systems in place, and fail to evaluate how CGMP systems are working for the production of individual dietary supplement products that are marketed. The FDA already has a voluntary program to recognize “accreditation bodies” that have the responsibility of accrediting third-party “certification bodies” to conduct safety audits for food products,<sup>124</sup> but questions remain about how the FDA could or would apply a similar program to ease their dietary supplement audit burden. Finally, questions remain about the accountability third-party auditors would have should a manufacturer or product receive a violation citation following their inspection. Considering these questions as well as how authorized third-party dietary supplement audits could overlap with facets of the proposed risk-based paradigm, **USP encourages exploring mechanisms, including third-party audits— where audit standards are based on CGMP, USP Quality Standards, and FDA-established criteria— and leveraging existing FDA programs in new ways to enable more audits of dietary supplement manufacturing facilities and products.**

## Increasing FDA resources is a necessary component of dietary supplement reform

Currently, the FDA faces challenges to overseeing the rapidly growing dietary supplement industry. Although more products enter the market each year, the FDA can only dedicate a small percentage of its resources to regulating the dietary supplement industry.<sup>76</sup> In a typical year, the FDA conducts about 500 to 600 dietary supplement inspections, which represents approximately 5 percent of manufacturing facilities<sup>125</sup> with the caveat that the FDA does not have comprehensive knowledge of all dietary supplement manufacturers.<sup>76</sup> With violations documented in over half of recently inspected dietary supplement manufacturers,<sup>56,126</sup> and known limitations in inspection capacity, additional resources for FDA inspections are necessary.

Furthermore, reports indicate that the FDA lacks the resources for more frequent inspections, expansive surveillance, and more frequent enforcement actions.<sup>64</sup> An important consideration for any legislative, regulatory, or policy reform and modernization is providing adequate resources for enforcement. All consumers will benefit from a regulatory framework that promotes product quality and provides appropriate tools and resources for the FDA to maintain appropriate oversight.<sup>45</sup> In the interests of public health and patient safety, **increasing FDA resources for the oversight of dietary supplements is necessary to appropriately oversee the growing dietary supplement sector.**

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## About USP

The U.S. Pharmacopeia (USP) is an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines, dietary supplements, and foods, through setting public quality standards in its various compendia. The *USP Dietary Supplements Compendium (DSC)* includes over 970 monographs and 190 general chapters for manufacturers and suppliers.<sup>123</sup> Additionally, USP provides services through its Dietary Supplements Verification Program.<sup>127</sup>

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