

REPORT 3 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (November 2020)
Dietary Supplements: Update on Regulation, Industry, and Product Trends
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. Patients and physicians expect the dietary supplements they purchase and recommend to be safe, quality products that are accurately labeled with their contents. Many dietary supplements, principally vitamins and minerals, are key components of modern evidence-based medicine for many conditions. However, illegal, fraudulent, adulterated and misbranded products can put patients at risk and adverse events (AEs) should be accurately collected. Additionally, confusion exists, for both patients and their caregivers, related to the regulation of dietary supplements and herbal products. The Council on Science and Public Health initiated this report to bring renewed attention to this important topic that affects many patients and to offer recommendations to strengthen AMA policy related to the dietary supplements.

Methods. English-language articles were selected from a search of the PubMed database through February 2020 using the search term “dietary supplement(s).” Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society and international, national, and local government agency websites were conducted to identify clinical guidelines, position statements, and reports.

Results. While millions of patients use dietary supplements regularly, the current regulatory structure in place for dietary supplements does not offer adequate protection to the public. In the 26 years since the passage of the Dietary Supplement Health and Education Act (DSHEA), the dietary supplement industry has been reshaped by a complex global supply chain, the Internet, and newly discovered ingredients of unknown safety. An estimated 75,000 new supplement products have been introduced since 1994, and the U.S. Food and Drug Administration (FDA) has received adequate safety data for fewer than 250 new ingredients. The FDA also has no way to determine what ingredients are contained in the tens of thousands of products on the market. Furthermore, with violations identified in over half of inspected dietary supplement manufacturers, more effective enforcement tools are required to protect the health of patients. All patients would benefit from a regulatory framework that promotes product safety and provides appropriate tools and resources for the FDA to maintain appropriate oversight.

Conclusion. The advancement of a safe and transparent dietary supplement marketplace will require a trustworthy supply chain and will involve robust AE, drug interaction, and tainted product reporting. Unethical individuals and companies engage in the manufacture and distribution of intentionally adulterated, misbranded, and improperly labeled dietary supplement products and pose significant risks to patient health and safety. The reliance on an industry that self regulates is insufficient and ineffective at protecting the health of patients. As the dietary supplement industry continues to grow and patients continue to use dietary supplements, efforts to revise and modernize FDA oversight of the industry and the DSHEA itself are necessary. A mandatory product registry would be a simple, low-burden way for the FDA and patients to obtain a complete picture of the marketplace and better protect public health by providing greater transparency, enabling prioritization of limited agency resources, and enhancing efforts to respond to emerging safety concerns. Additionally, both physician and patient education are paramount to understand this industry and the risks associated with dietary supplement products.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3, November 2020

Subject: Dietary Supplements: Update on Regulation, Industry, and Product Trends

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Referred to: Reference Committee E

1 INTRODUCTION

2
3 Patients and physicians expect the dietary supplements they purchase and recommend to be safe,
4 quality products that are accurately labeled with their contents. Many dietary supplements,
5 principally vitamins and minerals, are key components of modern evidence-based medicine for
6 many conditions. However, illegal, fraudulent, adulterated and misbranded products can put
7 patients at risk. Adverse events (AEs) can occur with use of dietary supplements, and when they
8 do, they should be accurately collected, tabulated and analyzed. Additionally, confusion exists, for
9 both physicians and patients, related to the regulation of dietary supplements and herbal products.

10
11 The Council on Science and Public Health initiated this report to bring renewed attention to this
12 important topic that affects many patients and to offer recommendations to strengthen American
13 Medical Association (AMA) policy related to the dietary supplements.

14 BACKGROUND

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16
17 The dietary supplement industry has grown from approximately 4,000 products in 1994 to as many
18 as 90,000 in 2017, according to some estimates.^{1,2} Surveys indicate that over half of Americans
19 consume dietary supplement products.^{3,4} Additionally, with the recent surge in the cannabidiol
20 (CBD) market, which absent a clear regulatory pathway already includes a substantial number of
21 products sold as dietary supplements, the number of products sold is expected to continue to
22 increase. The economic value of the industry is projected to reach nearly \$60 billion in the United
23 States, and nearly \$200 billion worldwide, by 2025.^{5,6}

24
25 As the industry grows and more individuals are using dietary supplement products, a renewed
26 focus on the risks associated with these products and the regulatory processes involved in bringing
27 them to market is warranted. This report will provide an overview of the current regulatory
28 framework for dietary supplements and comment on research-related activities, the dietary
29 supplement industry, and product trends.

30 METHODS

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32
33 English-language articles were selected from a search of the PubMed database through February
34 2020 using the search term “dietary supplement(s)” alone and coupled with “drug interactions” and
35 “regulation.” Additional articles were identified from a review of the references cited in retrieved
36 publications. Searches of selected medical specialty society and international, national, and local
37 government agency websites were conducted to identify clinical guidelines, position statements,
38 and reports.

1 DIETARY SUPPLEMENT REGULATION

2
3 *Dietary Supplement Health and Education Act*

4
5 The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a dietary supplement as a product,
6 taken orally, containing a dietary ingredient intended to supplement the diet.⁷ Dietary ingredients
7 include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes,
8 organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates
9 of the listed items.⁸ Dietary supplements come in many forms, including tablets, capsules, powders,
10 energy bars, and liquids and are available for purchase over-the-counter in stores throughout the
11 United States and via the Internet. Herbal supplements are considered a type of dietary supplement
12 and are included in this definition.

13
14 Since, by statutory definition, dietary supplements are only intended to supplement the diet, they
15 are not therapeutic medications and are not intended to treat, diagnose, mitigate, prevent, or cure
16 diseases. The U.S. Food and Drug Administration (FDA) oversees not only “conventional” food
17 products and medications but also dietary supplements. Dietary supplements are regulated by the
18 FDA differently from foods and differently from drugs. Whether a product is classified as a dietary
19 supplement, conventional food, or drug is based on its intended use, and most often, classification
20 as a dietary supplement is determined by the information that a manufacturer provides.
21 Medications go through a rigorous FDA approval process before entering the market; drugs are
22 considered unsafe until evidence shows they are safe. Dietary supplements do not undergo this
23 approval process and are considered safe until proven unsafe.

24
25 FDA regulates the processing, manufacturing, labeling, and packaging of dietary supplements
26 through the Dietary Supplement Health and Education Act (DSHEA), enacted as an amendment to
27 the FD&C Act in 1994.⁹ Dietary supplement companies are responsible for having evidence that
28 their products are safe, and that the label claims are truthful and not misleading. As long as the
29 product does not contain a “new dietary ingredient (NDI),” the company does not have to provide
30 safety evidence to the FDA before the product is marketed. The term NDI means a dietary
31 ingredient that was not marketed in the United States in a dietary supplement before October 15,
32 1994; however, no authoritative list of ingredients marketed before October 15, 1994 exists.¹⁰
33 Therefore, manufacturers and distributors, and not federal regulators, are responsible for
34 determining if an ingredient is an NDI.

35
36 Under DSHEA, manufacturers and distributors of dietary supplements and dietary ingredients are
37 prohibited from marketing products that are adulterated or misbranded. Manufacturers are
38 responsible for labeling their products before marketing to ensure that they meet all the
39 requirements of DSHEA and FDA regulations. The FDA is responsible for taking action against
40 any adulterated or misbranded dietary supplement product only after it reaches the market and a
41 violation is found. The FDA pursues enforcement actions on dietary supplement products for the
42 following reasons:

- 43
44
- 45 • Safety: The presence of unsafe ingredients or composition is generally determined from
46 postmarket surveillance, such as monitoring adverse event reports (AERs), to identify
47 potential concerns.¹¹
 - 48 • Manufacturing violations: Manufacturers must follow current good manufacturing practice
49 (cGMP) to ensure the identity, purity, strength, and composition of their products.
 - 50 • Marketing and misbranding (shared authority with the Federal Trade Commission (FTC)):
51 Once a dietary supplement is on the market, it is the responsibility of the FDA to monitor
product labels and package insert information to make sure that the information is accurate

1 and that any claims made are truthful and not misleading. The FDA, however, has limited
2 resources to effectively do this.

3
4 Some penalties and enforcement actions exist which the FDA is able to pursue in instances of
5 safety and cGMP violations. These include administrative actions such as warning letters, civil
6 penalties such as product recalls and injunctions, and criminal penalties including both
7 misdemeanor offenses of up to 1 year in prison and \$500,000 in fines, and felony offenses of up to
8 3 years in prison and \$500,000 in fines. Enforcement of penalties for marketing and misbranding is
9 a shared authority with FTC, and the FDA cannot impose penalties if the only violation is
10 misbranding. Civil penalties under the FDA include injunctions and product recalls, and under FTC
11 include administrative actions, injunctions, and fines for consumer relief and recovery of illegal
12 profits.

13 14 *Dietary Supplement Labeling*

15
16 Dietary supplement marketing, labeling, and advertising are all covered by regulations enforced by
17 both the FDA and the FTC. Unlike drugs, supplements are not intended to treat, diagnose, prevent,
18 or cure diseases. The FTC acts as the primary regulator of dietary supplement advertising and the
19 FDA possesses primary enforcement responsibility for dietary supplement claims made in
20 “labeling.”

21
22 The Nutrition Labeling and Education Act of 1990 gave the FDA the discretion to regulate health
23 claims for foods and dietary supplements and DSHEA made manufacturers responsible for
24 ensuring dietary supplements have appropriate labeling that reflects safety and efficacy. Three
25 classes of claims can legally be used on the labels of dietary supplements:¹²

- 26
27 1. Health claims: Statements that relate the consumption of a dietary ingredient to a reduced
28 risk of a disease or health-related condition. Health claims require authorization by the
29 FDA, but once a claim has been approved, it may be used by all manufacturers according
30 to the regulations established by the FDA (example: “Adequate calcium throughout life, as
31 part of a well-balanced diet, may reduce the risk of osteoporosis.”).
- 32 2. Nutrient content claims: Provide information on the level of a nutrient in a product in
33 absolute terms or relative to another component and help ensure that descriptive terms,
34 such as high or low, are used consistently for all types of dietary supplement products and
35 are meaningful to consumers. Most nutrient content claim regulations apply only to those
36 nutrients that have an established Daily Value (DV). Percentage claims for dietary
37 supplements are used to describe the percentage level of a dietary ingredient in a dietary
38 supplement and may refer to dietary ingredients for which there is no established DV.
39 Nutrient content claims require FDA review before they can be used on a product
40 (example: “40% omega-3 fatty acids, 10 mg per capsule”).
- 41 3. Structure/function claims: Describe the effect a substance has on the structure or function
42 of the body. These types of claims are not pre-approved by the FDA, but manufacturers
43 must have substantiation that the claim is truthful and not misleading and must submit a
44 notification with the text of the claim to FDA no later than 30 days after marketing the
45 dietary supplement with the claim. If a dietary supplement label includes such a claim, it
46 must state in a disclaimer (using wording that is specified in the DSHEA) that the FDA has
47 not evaluated the claim. The disclaimer must also state that the dietary supplement product
48 is not intended to “diagnose, treat, cure or prevent any disease,” because only a drug can
49 legally make such a claim. Structure/function claims may not explicitly or implicitly link
50 the claimed effect of the nutrient or dietary ingredient to a disease or to a state of health
51 leading to a disease (example: “Helps improve memory.”).

1 Another class of claim, a disease claim, is a claim to diagnose, cure, mitigate, treat, or prevent
2 disease; as noted, such claims are prohibited on dietary supplements and require FDA approval to
3 be used on approved drug products (example: “Reduces the pain and stiffness associated with
4 arthritis.”).

5
6 Criteria for the rigor of evidence needed to support a claim have not been established; scientific
7 evidence may be provided by just one article assessing a compound *in vitro* that has not achieved
8 recognition or agreement.¹³ Importantly, studies have shown consumers are generally unaware of,
9 or ignore, DSHEA disclaimers; studies also note that these disclaimers fail to communicate that
10 patients should use caution in interpreting the efficacy claims manufacturers make for their dietary
11 supplement and they have little reliable impact on patients’ beliefs about the risk and effectiveness
12 of dietary supplements. Furthermore, there is evidence that consumers erroneously believe that the
13 labels of dietary supplements will include warnings of adverse effects where appropriate.^{13,14}

14
15 While DSHEA, via statutory authority granted to the FDA, applies exclusively to the labeling of
16 dietary supplements, the FTC is primarily responsible for the regulation of dietary supplement
17 advertisements. The FTC regulates “unfair methods of competition” in commerce and “unfair or
18 deceptive” practices under Sections 5 and 12 of the Federal Trade Commission Act (FTCA). Two
19 principles apply in FTC enforcement of advertisements: ads have to be (1) truthful and not
20 misleading and (2) substantiated. Additionally, the FTC has the authority to compel manufacturers
21 to submit their evidence in substantiation of the claims they make in advertisements. Cease and
22 desist orders not only prohibit further deceptive practice but may require companies to pay a fine of
23 \$16,000 per ad per day in the instance of future violations. Cases have been rare; over the last
24 decade, the FTC reports that it has filed 120 cases challenging health claims made for dietary
25 supplements.¹⁵

26 27 *Supplement Facts Panel*

28
29 In May 2016, a final rule was published in the Federal Register detailing Revision of the Nutrition
30 and Supplement Facts Labels.¹⁶ The Supplement Facts label is the black and white box located on
31 dietary supplement product containers that is intended to provide the chemical composition of a
32 dietary supplement. Because of changes and evolution of the American diet and advancements in
33 nutrition science, federal requirements for the label are being updated. Notable changes include
34 updates to DV to reflect the current American diet; a change from reporting some vitamins in
35 International Units (IU) to more commonly used measures of milligrams (mg) and micrograms
36 (mcg); listing of folic acid as folate (measured in mcg of dietary folate equivalents); and listing of
37 the amount of added sugar and percent DV. The deadline for large manufacturers to reflect the
38 label changes was January 1, 2020. Smaller manufacturers have until January 1, 2021 to comply
39 with these changes. A resource has been developed to educate consumers about the changes.¹⁷

40
41 The FDA requires manufacturers to list all of the ingredients in a dietary supplement on the
42 Supplement Facts panel of the product, along with the amount of each by weight, except when the
43 ingredients are part of a “proprietary blend.”¹⁸ A proprietary blend (or “complex,” matrix,” or
44 “formulation”) is a collection of ingredients often unique to a particular product and sometimes
45 given a fanciful name. The specific amount of each individual ingredient in a proprietary blend
46 does not have to be listed; however, the absence of a stated amount for each ingredient can have
47 significant implications for patients and physicians, especially if the blend contains stimulant or
48 stimulant-like ingredients or if the ingredient has a supplement-drug interaction with a patient’s
49 medication.

1 *DSHEA Modernization and Product Registries*

2
3 The FDA recently announced efforts to strengthen the regulation of dietary supplements by
4 modernizing and reforming their oversight.¹⁹ The Agency established a Dietary Supplement
5 Working Group at the FDA to identify opportunities across the Agency to modernize the oversight
6 of dietary supplements, develop a new rapid-response tool to alert the public of tainted or recalled
7 products, foster the submission of NDI notifications so they can evaluate the safety of a new
8 ingredient before it becomes available to consumers, update the compliance policy regarding NDIs,
9 and engage in conversations to modernize DSHEA. A public meeting was held in May 2019,
10 attended by a representative from the AMA, to discuss Responsible Innovation in Dietary
11 Supplements; the stated purpose of the public meeting was to give interested parties an opportunity
12 to present ideas for facilitating responsible innovation in the dietary supplement industry while
13 preserving the FDA's ability to protect the public from unsafe, misbranded, or otherwise unlawful
14 dietary supplements.²⁰ The FDA has not yet released any reports or guidance from the public
15 meeting. Many stakeholders testified in support of appropriate enforcement tools and policies,
16 which may include mandatory recall and related authorities over products that are marketed as
17 dietary supplements but contain drugs or drug analogues; the utilization of risk-based inspections
18 for dietary supplement manufacturing facilities; and strengthening of AER systems.

19
20 Of note, a recent survey conducted by the Pew Charitable Trusts found that most American adults
21 believe the FDA should do more to ensure the safety of dietary supplements.^{21,22} Experts in the
22 field of dietary supplements and their regulatory structure support modernization and reform of
23 DSHEA to include stronger safeguards resulting in access to quality products.²³

24
25 Currently, the FDA has no mechanism to know what dietary supplement products are on the
26 market. Because dietary supplement manufacturers are not required to submit product information,
27 the FDA has limited knowledge about the products on the market, including their ingredients and
28 the conditions under which they were manufactured. Several experts and organizations support the
29 concept of an FDA product listing regime--if it can be effective at identifying and removing
30 dangerous dietary supplement products from the marketplace.²⁴ Some features have been proposed
31 for a mandatory product registry to safeguard the public and inform physicians, investigators, and
32 regulators including linking each product to a unique identifier such as a stock keeping unit (SKU)
33 barcode or QR code and the ability to flag all products produced by manufacturers who have
34 received warning letters from the FDA.²⁵ Proponents of an FDA-managed, mandatory product
35 registry also support giving the FDA additional authorities to decline to add labels to the registry if
36 the label lists a prohibited ingredient as well as FDA-required investigations of products labeled as
37 containing NDIs for which no evidence of safety exists or for products which have reports of
38 undisclosed ingredients.

39
40 The Supplement OWL® (Online Wellness Library) dietary supplement product listing is an
41 industry-wide initiative developed with the intent to create a more complete picture of the
42 marketplace and is led by the Council for Responsible Nutrition, joined by the American Botanical
43 Council, the American Herbal Products Association, the Consumer Healthcare Products
44 Association, the Natural Products Association, and the United Natural Products Alliance. However,
45 the Supplement OWL is voluntary for manufacturers and is only a list of products; it lacks all of
46 the safety provisions recommended by experts and listed above to ensure a safer marketplace of
47 dietary supplements.²⁵

1 DIETARY SUPPLEMENT RESEARCH

2
3 DSHEA granted the authority to establish regulations regarding dietary supplement manufacturing,
4 regulate health claims and labeling of dietary supplements, and create governmental bodies to
5 encourage research on supplements, such as centers and offices at the National Institutes of Health
6 (NIH). Additionally, the FDA created a Botanical Safety Consortium, a public-private partnership
7 that will gather leading scientific minds from industry, academia, and government to promote
8 scientific advances in evaluating the safety of botanical ingredients and mixtures in dietary
9 supplements.

10
11 *National Institutes of Health*

12
13 The NIH supports research and provides educational materials on dietary supplements.²⁶ The NIH
14 Office of Dietary Supplements (ODS) provides scientific information about dietary supplements
15 with the stated mission to strengthen knowledge and understanding of dietary supplements.²⁷ ODS
16 hosts a website containing information about dietary supplement ingredients and co-funds research
17 grants with several other NIH centers, including the National Center for Complementary and
18 Integrative Health (NCCIH). ODS also supports the Dietary Supplement Label Database (DSLDD)
19 which includes label derived information from dietary supplement products marketed in the U.S.²⁸
20 DSLDD was developed to serve the research community and as a resource for health care providers
21 and the public. It also contains archived labels from products that have been removed from the
22 market. Research suggests that even these NIH resources do not provide accurate information
23 about the contents of dietary supplements for researchers or clinicians.²⁹

24
25 DIETARY SUPPLEMENT INDUSTRY

26
27 *Product Supply Chain and Quality*

28
29 Beyond oversight by FDA and related agencies, the dietary supplement industry, can, and should,
30 play an active and influential role in addressing dietary supplement quality and the problems
31 associated with bad actors within the industry. The FDA inspected 656 dietary supplement
32 production facilities in fiscal year 2017 and found violations in over half of them. The most
33 common violations include failing to establish the identity, purity, strength, or composition of the
34 final product.³⁰ Many companies do follow cGMP, adequately self-regulate, and make every effort
35 to produce quality products, yet it is well documented in literature that unethical individuals and
36 companies continue to engage in the manufacture and distribution of low quality, intentionally
37 adulterated, or misbranded products labeled as dietary supplements that pose significant threats to
38 patient health and safety.³¹⁻³⁴

39
40 The supply chain behind the manufacture and distribution of dietary supplements can involve
41 multiple ingredient suppliers, brokers, and contract manufacturers, both inside and outside of the
42 United States. Because the supply chain is long and involves many links, problems with dietary
43 supplement products can arise at various points and it can be difficult to track the lineage of
44 ingredients and the identities of parties involved in the production of a single product.

45
46 Within the industry supply chain, ingredient providers, brokers, product manufacturers, distributors
47 and product marketers all have the responsibility to self-regulate through qualifying and validating
48 their suppliers, ensuring a secure supply chain, testing ingredients and finished products,
49 identifying and removing high-risk products from product assortments, and implementing other
50 mechanisms to assure that ingredients and final products do not contain undisclosed illegal
51 ingredients with the potential to harm patients. Makers of fraudulent products ignore legal

1 obligations and FDA lacks the resources for more frequent inspections, substantive surveillance,
 2 and enforcement of the law.³⁵

3
 4 A regulatory framework that helps promote safe, quality dietary supplement products is necessary.
 5 Experts have suggested efforts are needed from both the FDA and industry to increase
 6 manufacturer awareness of cGMP regulations and quality standards, including quality control
 7 specifications for the identity, purity, strength, and composition of finished dietary supplements as
 8 well as their ingredients. Wider use of the public standards developed by the United States
 9 Pharmacopeial Convention (USP) or other public compendial standards, along with following
 10 cGMP, has been recommended for dietary supplements.³⁶ USP has also developed a General
 11 Chapter, <2251> Adulteration of Dietary Supplements with Drugs and Drug Analogs to assist
 12 manufacturers.³⁷

13
 14 *Product Testing*

15
 16 With the large increase in dietary supplement manufacturers and the subsequent rise in dietary
 17 supplement safety concerns, several companies have started independent product certification
 18 services to provide an additional level of security and risk minimization for consumers who rely on
 19 dietary supplement products. Many companies test products to verify they contain the labeled
 20 dose(s) of the active ingredient(s) and not to contain microbes, heavy metals, other toxins, and/or
 21 substances that are banned by athletic organizations.³⁸ Testing labs include ConsumerLab.com,³⁹
 22 USPharmacopeia,⁴⁰ NSF International,⁴¹ and UL.⁴²

23
 24 Additional resources exist for patients and physicians who are seeking more information about
 25 products, product ingredients, or products with reported violations (Box 1). USP provides a list of
 26 products they have independently verified for quality,⁴⁰ NSF has a listing of products that are NSF
 27 Certified for Sport®,⁴¹ and the U.S. Antidoping Agency (USADA) hosts a resource for dietary
 28 supplement safety education and awareness, Supplement 411.⁴³ Additionally, other, more
 29 comprehensive resources exist, but may require a paid subscription. An example is the Natural
 30 Medicines Research Collaboration Natural Medicines database, which claims to contain over 1200
 31 monographs on natural ingredients, including vitamins, herbs, minerals, non-herbal supplements,
 32 naturally sourced chemical compounds, and foods; Natural Medicines provides monographs that
 33 include information on a variety of topics including interactions for both health care professionals
 34 and patients.⁴⁴

35
 36 DIETARY SUPPLEMENT PRODUCT TRENDS

37
 38 *General Trends*

39
 40 Not all dietary supplements lack evidence of efficacy. Many products considered dietary
 41 supplements are an important part of patient health care, including products to treat vitamin and
 42 mineral deficiencies and supplementation during pregnancy. However, many products that have
 43 medical benefits are commonly overused among the general population in an attempt to improve or
 44 maintain health and use in these ways provides little benefit. Studies have noted that dietary
 45 supplement use was not associated with mortality benefits in a nationally representative sample of
 46 U.S. adults, that supplement use itself does not have direct health benefits, and in some cases
 47 excess intake might increase harmful effects, including cancer and mortality.^{38,45} Only
 48 approximately a quarter of patients who are using dietary supplements are doing so based on the
 49 recommendation of their physician.⁴⁶ Additionally, a study commissioned by the FTC found that
 50 the majority of patients in the United States are overly optimistic about the results they can
 51 achieve¹³

1 Investigators have also commented on significant misperceptions of understanding related to the
 2 safety and efficacy of dietary supplements and FDA authorities. Investigators found that patients
 3 incorrectly believe that dietary supplements are approved by the government; that dietary
 4 supplements have been tested for safety and effectiveness; that the content of all dietary
 5 supplements are analyzed; and that manufacturers are required to disclose known adverse effects.¹⁴
 6 Each of these beliefs is a misconception.

7
 8 Experts on the subject of dietary supplements note that patients may not be aware of the lack of
 9 efficacy of products and respond to advertisements, recommendations from friends and family, and
 10 longstanding habits of use. Consistently, mainstream media produces articles related to popular
 11 dietary supplements. At the beginning of each new year, it is common to see many lists about
 12 dietary supplement trends for the year ahead, whether based on evidence of efficacy or not. Lists of
 13 dietary supplement trends for 2020 include bone marrow, berberine, nootropic products, collagen
 14 peptides, and cannabidiol (CBD).^{47,48} Brain enhancement (nootropic) dietary supplement products
 15 are an emerging and increasing problem, as many contain unapproved pharmaceutical products.⁴⁹
 16 The Council on Science and Public Health recently commented on this emerging issue in CSAPH
 17 report 9-A-16, Increasing Awareness of Nootropic Use.⁵⁰

18
 19 *Commonly Adulterated Products*

20
 21 Adulteration of dietary supplements is usually either economic adulteration, when a less expensive
 22 ingredient is used in place of a more expensive ingredient listed on the label, or pharmaceutical
 23 adulteration, when an active pharmaceutical is included in a product and not listed on the label.³⁴
 24 Adding to the complexity and safety risks associated with adulteration, pharmaceutical adulteration
 25 includes the use of not only FDA-approved drugs, or drugs formerly approved by the FDA and
 26 withdrawn, but also drugs used in other countries (and never FDA-approved), and experimental
 27 drugs minimally or never tested in humans.^{51,52}

28
 29 Dietary supplements are associated with an estimated 23,000 emergency department visits each
 30 year, and many of these visits are due to products that are adulterated with pharmaceutical drugs.
 31 The most commonly adulterated dietary supplements are those marketed as weight loss, sexual
 32 enhancement, or sports supplements.^{33,34,53-57} Many times, active pharmaceuticals are identified in
 33 dietary supplements even after FDA warnings to the manufacturer.^{52,58} The drug ingredients in
 34 these dietary supplements have the potential to cause AEs related to accidental misuse, overuse,
 35 interaction with other medications, or with other pharmaceuticals within the supplement, and
 36 related to underlying health conditions in the user.⁵⁹

37
 38 Additionally, extensive efforts have been made to silence physician-researchers investigating
 39 adulterated dietary supplements.^{60,61} Despite research being vetted through peer review and
 40 published in reputable journals, dietary supplement manufacturers have attempted to intimidate
 41 researchers with strategic lawsuits against public participation (SLAPP), which attempt to suggest
 42 research was biased, unethical, or vindictive, instead of publishing rebuttals to challenge the
 43 research. Although anti-SLAPP laws exist and are intended to prevent people from using courts,
 44 and even the threat of a lawsuit, to intimidate people who are exercising their First Amendment
 45 rights, some courts have allowed these lawsuits go to trial to not undermine a supplement
 46 company's constitutional right to a jury trial.

47
 48 *Cannabidiol*

49
 50 CBD is a major cannabinoid in marijuana and does not appear to have any psychoactive effects
 51 similar to those caused by Δ^9 -tetrahydrocannabinol (THC). Most cannabinoid compounds are

1 derived from the plant genus cannabis. Various breeds or strains of cannabis for medicinal use have
2 a significant variety in the ratios of CBD-to-THC and are known to contain other non-psychoactive
3 cannabinoids. “Marijuana” is listed as a Schedule 1 controlled substance under the Controlled
4 Substances Act (CSA); CBD and other components of cannabis are also Schedule 1 compounds by
5 definition because they are considered “derivatives” or “components” of marijuana.
6

7 Hemp, however, is excluded from this rule since the Agricultural Improvement Act (the 2018 Farm
8 Bill) removed hemp-derived products from Schedule I status under the CSA.⁶² The Farm Bill
9 defined hemp as a strain of the cannabis plant containing no more than 0.3% THC. The 2018 Farm
10 Bill does not legalize CBD generally and CBD remains a Schedule 1 substance under the CSA. The
11 2018 Farm Bill does create exceptions to this Schedule 1 status in certain situations: any
12 cannabinoid that is derived from hemp will be legal, if and only if that hemp is produced in a
13 manner consistent with the Farm Bill, associated federal regulations, associated state regulations,
14 and is produced by a licensed grower. All other cannabinoids, produced in any other setting,
15 remain a Schedule I substance under the CSA and are illegal. The one exception is pharmaceutical-
16 grade CBD products that have been approved by the FDA, of which there is one. Epidiolex from
17 GW Pharmaceuticals, a purified 98% oil-based CBD extract of known and constant composition, is
18 FDA approved to treat rare forms of epilepsy, and is Schedule V.
19

20 The legal landscape of CBD remains complex. As states have legalized cannabis use for medical
21 purposes and for any purpose, a variety of non-FDA approved or regulated products have become
22 more mainstream. Among these products are CBD oils or other products rich in CBD. CBD
23 products are used by the public for a variety of purported indications, including seizure reduction,
24 as an anti-inflammatory, and for alleviating anxiety. Often, CBD products are (incorrectly) called
25 CBD-only products; many states define “CBD-only” as containing less than 0.3% THC (the same
26 as hemp). For many products, it is difficult to determine if the product is hemp-derived (Schedule 1
27 exempt) or not, and variability in CBD and THC content is common. Recently, an analysis of
28 twenty popular CBD products and found that only three contained what was listed on the labels.⁶³
29

30 The FDA has taken the position that CBD cannot be legally sold in either supplements or foods and
31 has repeatedly said it needs more data to better understand the risks and benefits of CBD.^{64,65} The
32 FDA has estimated it could take between three and five years to complete a rulemaking process
33 that would allow CBD to be added to food and dietary supplements. If it is eventually permitted,
34 FDA will need to establish science-based standards for dosing, composition, nomenclature, product
35 claims, and numerous other manufacturing and marketing issues to further the goals of protecting
36 the public and providing more clarity to industry and the public.^{66,67} To further progress the
37 knowledge related to CBD, the FDA has re-opened a public docket indefinitely for the submission
38 of scientific data related to CBD.⁶⁷
39

40 The FDA has focused its limited enforcement resources on removing CBD products that make
41 claims of curing or treating disease, leaving many CBD products on the market as both foods and
42 dietary supplements available for sale. Some experts believe this is an opportunity for the FDA to
43 reform and improve oversight of dietary supplements and ingredients to create clear, reasonable
44 pathways for low-dose CBD and other new substances to be safely introduced into supplements
45 and food.⁶⁵
46

47 Widespread agreement exists that additional research is needed regarding CBD, both for efficacy
48 and long-term safety. Currently, CBD and hemp oils remain a widely available but unproven
49 therapeutic option for many patients. CBD became the top selling “dietary supplement” in the
50 United States in 2018 according to a recent report from the American Botanical Council.⁶³ Experts
51 note that physicians should remain open to the possible future role CBD products may play in the

1 management of a variety of difficult to treat diseases,⁶⁸ yet use caution and consider of the risks
2 present in patients' use of CBD products and the possibility of product contamination.⁶⁹

3 4 ADVERSE EVENT REPORTING, INTERACTIONS, AND PRODUCT REPORTING

5
6 Post-market surveillance is a key part of identifying safety problems associated with both
7 pharmaceutical products and dietary supplement products. The FD&C Act defines a dietary
8 supplement AE as "any health-related event associated with the use of a dietary supplement that is
9 adverse" (e.g., headache, abdominal pain, allergic reaction, rash, and dizziness or lightheadedness).
10 A serious adverse event (SAE) is defined as an AE that "results in death, a life-threatening
11 experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a
12 congenital anomaly or birth defect; or requires, based on a reasonable medical judgement, a
13 medical or surgical intervention to prevent an outcome described above."⁷⁷

14
15 While few of the many high-quality studies evaluating dietary supplements and ingredients looking
16 for positive health benefits from their use have found such results, several studies have produced
17 evidence of harm.⁴⁶ It has been reported that less than 40 percent of patients reveal use of dietary
18 supplements to their health care professionals and no metrics could be located related to how many
19 health care professionals directly ask patients about dietary supplement use. The US Government
20 Accountability Office estimates that a small fraction of the estimated 50,000 adverse reactions each
21 year from dietary supplements are reported to the FDA. The lack of reporting, along with the poor
22 quality of the information received in the few reports make it nearly impossible for the FDA to find
23 and remove dangerous supplements.^{70,71}

24
25 Literature documents that concomitant use of dietary supplements and prescribed medications is
26 common, problematic, and can result in life-threatening ADEs, hospitalizations, and fatalities.⁷²
27 Adding to the risk for patients, dietary supplements often contain multiple active ingredients and
28 are often inaccurately labeled. Myriad products and ingredients have been implicated in
29 interactions and ADEs, yet investigators note underreporting, lack of case reports, and incomplete
30 reports.^{23,72-76} In several instances, local public health departments, the Centers for Disease Control
31 and Prevention (CDC), or the Department of Defense have been more successful at linking cases of
32 illness to dietary supplement products than physician reporting and the FDA.⁷⁵

33
34 Suspected supplement-related AEs should be reported to the FDA.³⁸ All reporting by physicians is
35 voluntary and also strongly recommended; the FDA gives extra credence to physician reports and
36 the voluntary system of passive surveillance is the only opportunity the FDA has to detect harmful
37 dietary supplements. The Safety Reporting Portal (SRP)⁷⁷ streamlines the process of reporting
38 product safety issues to the FDA and the NIH, formerly done through FDA's Adverse Event
39 Reporting System (FAERS)⁷⁸ and MedWatch⁷⁹ Online Voluntary Reporting Form. The SRP can be
40 used by manufacturers, health care professionals, researchers, public health officials, and patients.⁸⁰
41 Contaminated dietary supplement products can be also be reported via an FDA portal.⁸¹ Box 2
42 provides a list of resources for reporting dietary supplement safety issues.

43
44 Some dietary supplements are known to cause clinically important interactions with drugs and
45 should be avoided by most patients receiving any pharmacologic therapy. Many other dietary
46 supplement products, however, are predicted to cause interactions based limited in vitro studies.^{72,82}
47 Additionally, some dietary supplements have the potential to interfere with laboratory results.⁸³
48 Risk-based and open conversation with patients is crucial in minimizing and appropriately
49 identifying interactions.

1 PATIENT-PHYSICIAN INTERACTION

2
3 Physicians or their office staff should include discussion of dietary supplements when reviewing
4 medications with all patients. Reporting suspected AEs related to dietary supplements is critical,
5 and dietary supplements should also be considered as source of unexplained AEs. Risk-based
6 patient counseling of patients should include discussion about the variable quality of dietary
7 supplements, the presence of un reputable products in the marketplace, and information on which
8 products are commonly adulterated; additionally, physicians can ask patients to bring dietary
9 supplement products with them to appointments for review and discussion.⁵² Physicians should
10 also make an effort to evaluate any potential drug-supplement interactions based on the products
11 patients are using or considering. Box 1 contains a list of resources for information about dietary
12 supplement products.

13
14 When counseling patients about dietary supplements, it should be noted that supplementation is not
15 a substitute for a healthful and balanced diet and, in most cases, provides little benefit. Targeted
16 supplementation may be warranted for high-risk populations for whom nutritional requirements
17 may not be met through diet alone, including people at certain life stages and those with specific
18 risk factors.³⁸

19
20 CURRENT AMA POLICY AND ACTIVITIES

21
22 AMA currently has policy related to dietary supplements. Policy H-150.954, “Dietary Supplements
23 and Herbal Remedies,” notes AMA’s support of the FDA MedWatch program, encourages the
24 reporting of adverse events associated with dietary supplements, and urges manufacturers to
25 investigate and include on the label any adverse effects, contraindications, and possible drug
26 interactions. Policy D-150.991, “Herbal Products and Drug Interactions,” supports FDA efforts to
27 create a publicly accessible database of adverse event and drug interaction information on dietary
28 supplements. Policy H-150.954 also urges for modifications to strengthen DSHEA, supports FDA
29 and FTC enforcement efforts, and supports appropriate dietary supplement labeling. This policy
30 also notes the AMA’s support of educating patients and physicians about the risks associated with
31 dietary supplements. Policy H-150.946, “Advertising for Herbal Supplements,” states that the
32 naming, packaging, and advertising of dietary supplement products be such that they cannot be
33 confused with pharmaceutical products. Policy H-115.988, “Qualitative Labeling of All Drugs,”
34 supports efforts to require both active and inactive ingredients of over-the-counter and prescription
35 drugs and dietary supplements to be listed on the manufacturer’s label or package insert. Policy
36 D-120.982, “Illegal Online Prescribing Operations,” supports efforts that help the Drug
37 Enforcement Administration and the FDA to better regulate and control the illegal online sales and
38 distributions of drugs, dietary supplements, and herbal remedies.

39
40 Additionally, the AMA is a member of the Dietary Supplement Quality Collaborative (DSQC), a
41 group committed to the advancement of policies and initiatives designed to improve and maintain
42 the quality and safety of products marketed as dietary supplements.⁸⁴ The DSQC supports policies
43 and resources to advance innovation; help ensure safe, quality supplements; remove illegal and
44 tainted products from the marketplace; and promote consumer education. To this end, through
45 DSQC, AMA has contributed to the writing of a white paper seeking to educate stakeholders about
46 the dangers of tainted dietary supplements and recommend solutions to aid in minimizing the risks
47 associated with them.³⁵ The AMA has also been a signatory to letters requesting support for the
48 FDA’s Office of Dietary Supplement Programs.

1 SUMMARY

2
3 Millions of patients use dietary supplements yet today, the regulatory structure in place for dietary
4 supplements does not adequately protect the public. In the 26 years since the passage of DSHEA,
5 the dietary supplement industry has been reshaped by a complex global supply chain, the Internet,
6 and newly discovered ingredients of unknown safety. An estimated 75,000 new supplement
7 products have been introduced since 1994, and the FDA has received adequate safety data for
8 fewer than 250 new ingredients. The FDA also has no way to determine what ingredients are
9 present in the tens of thousands of products on the market.^{23,24}

10
11 Furthermore, with violations in over half of inspected dietary supplement manufacturers,³⁰ more
12 effective enforcement tools are required to protect the health of patients. All patients will benefit
13 from a regulatory framework that promotes product safety and provides appropriate tools and
14 resources for the FDA to maintain appropriate oversight.³⁴

15
16 CONCLUSION

17
18 The advancement of a safe and transparent dietary supplement marketplace will require a
19 trustworthy supply chain and will involve robust AE, drug interaction, and tainted product
20 reporting. The reliance on an industry that self-regulates is insufficient and ineffective at protecting
21 the health of patients. Unethical individuals and companies engage in the manufacture and
22 distribution of intentionally adulterated, misbranded, and improperly labeled dietary supplement
23 products and pose significant risks to patient health and safety. As the dietary supplement industry
24 continues to grow and patients continue to use dietary supplement, efforts to revise and modernize
25 the DSHEA and FDA oversight of the industry and are necessary. The FDA has no mechanism to
26 know what dietary supplement products, containing what ingredients, are on the market. Some
27 have suggested that a mandatory product registry would be a simple, low-burden way for the FDA
28 and patients to obtain a complete picture of the marketplace and better protect public health by
29 providing greater transparency, enabling prioritization of limited agency resources, and enhancing
30 efforts to respond to emerging safety concerns. Additionally, both physician and patient education
31 are paramount to understand this industry and the risks associated with dietary supplement
32 products.

33
34 RECOMMENDATIONS

35
36 The Council on Science and Public Health recommends that the following be adopted and the
37 remainder of the report be filed:

- 38
39 1. That Policy H-150.954, “Dietary Supplements and Herbal Remedies” be amended by
40 addition and deletion to read as follows:

41
42 (1) Our AMA supports efforts to enhance U.S. Food and Drug Administration (FDA)
43 resources, particularly to the Office of Dietary Supplement Programs, to
44 appropriately oversee the growing dietary supplement sector and adequately
45 increase inspections of dietary supplement manufacturing facilities.

46
47 (2) Our AMA supports the FDA having appropriate enforcement tools and policies
48 related to dietary supplements, which may include mandatory recall and related
49 authorities over products that are marketed as dietary supplements but contain
50 drugs or drug analogues, the utilization of risk-based inspections for dietary

1 supplement manufacturing facilities, and the strengthening of adverse event
2 reporting systems.

3
4 (3) Our AMA supports continued research related to the efficacy, safety, and long-
5 term effects of dietary supplement products.

6
7 (4) Our AMA will work with the FDA to educate physicians and the public about
8 FDA's ~~MedWatch program~~ Safety Reporting Portal (SRP) and to strongly
9 encourage physicians and the public to report potential adverse events associated
10 with dietary supplements and herbal remedies to help support FDA's efforts to
11 create a database of adverse event information on these forms of
12 alternative/complementary therapies.

13
14 (5) Our AMA strongly urges physicians to inquire about patients' use of dietary
15 supplements and engage in risk-based conversations with them about dietary
16 supplement product use.

17
18 (6) Our AMA continues to strongly urge Congress to modify and modernize the
19 Dietary Supplement Health and Education Act to require that:

20 (a) dietary supplements and herbal remedies including the products already
21 in the marketplace undergo FDA approval for evidence of safety and
22 efficacy;

23 (b) dietary supplements meet standards established by the United States
24 Pharmacopeia for identity, strength, quality, purity, packaging, and
25 labeling;

26 (c) FDA establish a mandatory product listing regime that includes a unique
27 identifier for each product (such as a QR code), the ability to identify
28 and track all products produced by manufacturers who have received
29 warning letters from the FDA, and FDA authorities to decline to add
30 labels to the database if the label lists a prohibited ingredient or new
31 dietary ingredient for which no evidence of safety exists or for products
32 which have reports of undisclosed ingredients; and

33 (d) regulations related to new dietary ingredients (NDI) are clarified to
34 foster the timely submission of NDI notifications and compliance
35 regarding NDIs by manufacturers; and

36
37 (7) Our AMA supports FDA postmarketing requirements for manufacturers to report
38 adverse events, including drug interactions; and legislation that declares
39 metabolites and precursors of anabolic steroids to be drug substances that may not
40 be used in a dietary supplement.

41
42 (8) Our AMA will work with the Federal Trade Commission (FTC) to support
43 enforcement efforts based on the FTC Act and current FTC policy on expert
44 endorsements and supports adequate funding and resources for FTC enforcement
45 of violations of the the FTC Act.

46
47 (9) Our AMA strongly urges that criteria for the rigor of scientific evidence needed to
48 support a structure/function claim on a dietary supplement be established by the
49 FDA and minimally include requirements for robust human studies supporting the
50 claim.

- 1 (10) Our AMA strongly urges dietary supplement manufacturers and distributors to
2 clearly label all products with truthful and not misleading information and for
3 ~~supports that the product labeling of dietary supplements and herbal remedies to:~~
4 (a) ~~that bear structure/function claims contain the following disclaimer as a~~
5 ~~minimum requirement: “This product has not been evaluated by the~~
6 ~~Food and Drug Administration and is not intended to diagnose, mitigate,~~
7 ~~treat, cure, or prevent disease.” This product may have significant~~
8 ~~adverse side effects and/or interactions with medications and other~~
9 ~~dietary supplements; therefore it is important that you inform your~~
10 ~~doctor that you are using this product;~~
11 (a) not include structure/function claims that are not supported by evidence
12 from robust human studies;
13 (b) ~~should~~ not contain prohibited disease claims;
14 (c) eliminate “proprietary blends” and list and accurately quantify all
15 ingredients contained in the product;
16 (d) require advisory statements regarding potential supplement-drug and
17 supplement-laboratory interactions and risks associated with overuse and
18 special populations; and
19 (e) include accurate and useful disclosure of ingredient measurement.
20
21 (11) Our AMA supports and encourages the FDA's regulation and enforcement of
22 labeling violations and FTC's regulation and enforcement of advertisement
23 violations of prohibited disease claims made on dietary supplements and herbal
24 remedies.
25
26 (12) Our AMA urges that in order to protect the public, manufacturers be required to
27 investigate and obtain data under conditions of normal use on adverse effects,
28 contraindications, and possible drug interactions, and that such information be
29 included on the label.
30
31 (13) Our AMA will continue its efforts to educate patients and physicians about the
32 possible ramifications risks associated with the use of dietary supplements and
33 herbal remedies- and supports efforts to increase patient, healthcare practitioner,
34 and retailer awareness of resources to help patients select quality supplements,
35 including educational efforts to build label literacy.
36

- 37 2. That Policy H-120.926, “Expedited Prescription Cannabidiol Drug Rescheduling,” be
38 amended by addition and deletion to read as follows:
39

40 Regulation of Cannabidiol Products

41 Our AMA will: (1) encourage state controlled substance authorities, boards of pharmacy,
42 and legislative bodies to take the necessary steps including regulation and legislation to
43 reschedule U.S. Food and Drug Administration (FDA)-approved cannabidiol products, or
44 make any other necessary regulatory or legislative change, as expeditiously as possible so
45 that they will be available to patients immediately after approval by the FDA and
46 rescheduling by the U.S. Drug Enforcement Administration; ~~and~~ (2) advocate that an FDA-
47 approved cannabidiol medication should be governed only by the federal and state
48 regulatory provisions that apply to other prescription-only products, such as dispensing
49 through pharmacies, rather than by these various state laws applicable to unapproved
50 cannabis products; and (3) support comprehensive FDA regulation of cannabidiol products
51 and practices necessary to ensure product quality, including identity, purity, and potency.

- 1 3. That policy D-150.991, “Herbal Products and Drug Interactions,” that notes our AMA’s
2 support of FDA efforts to create a publicly accessible database of adverse event and drug
3 interaction information on dietary supplements, be reaffirmed.

Fiscal Note: Less than \$1000

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Box 1. Resources for dietary supplement product information.

1. [USP verified products](#) ⁴⁰
2. [NSF Certified for Sport® products](#) ⁴¹
3. [USADA Supplement 411](#) ⁴³
4. [Natural Medicines Research Collaboration Natural Medicines database](#) (paid subscription)⁴⁴

Box 2. Resources for reporting dietary supplement safety issues.

1. [The Safety Reporting Portal](#) (SRP) ⁷⁷
2. [Reporting Unlawful Sales of Medical Products on the Internet](#) ⁸¹
3. [How to Report a Problem with Dietary Supplements](#) ⁸⁰
4. [FDA's Adverse Event Reporting System \(FAERS\)](#) ⁷⁸
5. [MedWatch Online Voluntary Reporting Form](#) ⁷⁹