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Which Features of Dietary Supplement Industry, Product Trends, and Regulation Deserve Physicians' Attention?

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Abstract

Patients expect that dietary supplements they purchase—and physicians expect that dietary supplements they recommend—are safe, accurately labeled, quality products. Since many dietary supplements, especially vitamins and minerals, are key parts of evidence-based interventions for patients with many conditions, illegal, fraudulent, adulterated, or improperly labeled products should be regarded as sources of clinical and ethical concern. Adverse events (AEs) can occur and, when they do, relevant data should be carefully collected and analyzed. This article considers how many physicians' and patients' confusion about dietary supplement regulation can undermine quality caregiving and responses to AEs. This article also summarizes a recent American Medical Association Council on Science and Public Health report on dietary supplement supply and marketing practices and on physicians' roles in guiding patients when dietary supplement use is clinically indicated.

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Market Growth

The dietary supplement industry grew from approximately 4000 products in 1994 to as many as 90 000 in 2017, according to estimates.^{1,2} Surveys indicate that more than half of US adults consume dietary supplement products.^{3,4} The economic value of the industry is projected to reach nearly \$60 billion in the United States—and nearly \$200 billion worldwide—by 2025.^{5,6} As the industry grows and more individuals use dietary supplements, a renewed focus on the risks associated with these products and the **regulatory processes** involved in bringing them to market is warranted.

Regulation

The Federal Food, Drug, and Cosmetic (FD&C) Act defines a dietary supplement as a product, taken orally, containing a dietary ingredient intended to supplement the diet.⁷ Dietary supplements come in many forms—including tablets, capsules, powders, energy bars, and liquids—and are available for purchase over the counter in stores and via the internet. Dietary supplements are only intended to supplement the diet; they are not

therapeutic medications and are not intended to treat, diagnose, mitigate, prevent, or cure diseases. Dietary supplements are regulated by the US Food and Drug Administration (FDA) differently from “conventional” foods and drugs.⁸ Drugs go through a rigorous **FDA approval process** before entering the market; drugs are considered unsafe until evidence shows they are safe. Dietary supplements do not undergo this approval process and are considered safe until proven unsafe.

The FDA regulates the processing, manufacturing, labeling, and packaging of dietary supplements through the Dietary Supplement Health and Education Act (DSHEA), enacted as an amendment to the FD&C Act in 1994.⁹ Dietary supplement companies are responsible for having evidence that their products are safe and for ensuring that the label claims are truthful and not misleading. The FDA is responsible for taking action against any adulterated or misbranded dietary supplement product only after it reaches the market and a violation is found. The FDA pursues enforcement actions on dietary supplement products for safety issues, manufacturing violations, and improper marketing or misbranding, including the use of prohibited disease claims.^{8,10} While structure/function claims, which describe the effect a substance has on bodily structures or functions (eg, “helps improve memory”), are permitted, disease claims—or claims that a product can diagnose, cure, mitigate, treat, or prevent disease (eg, “reduces the pain and stiffness associated with arthritis”)—are prohibited on dietary supplement labels and require FDA approval and evidence to be used on labels of approved drug products.

The FDA recently announced efforts to strengthen the regulation of dietary supplements by modernizing and reforming their oversight.¹¹ A recent survey conducted by the Pew Charitable Trusts found that most American adults believe the FDA should do more to ensure dietary supplements’ safety, and experts support stricter regulation and reform of the DSHEA.^{12,13,14} Reform proponents support mandatory product listing that includes safety provisions^{15,16}; the Supplement OWL[®] is also a resource that can be improved.¹⁷

Supply Chain Opacity and Poor Quality

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 and compliance. The FDA inspected 656 dietary supplement production facilities in fiscal year 2017 and found violations in more than half of them, the most common violation being the failure to establish “purity, strength, or composition of their final product.”¹⁵ Although many companies adequately self-regulate, it is well documented that unethical individuals and companies continue to manufacture and distribute low-quality, adulterated, or misbranded products labeled as dietary supplements.^{18,19,20,21}

The supply chain link between manufacture and distribution of dietary supplements can involve multiple ingredient suppliers, brokers, and domestic and international contract manufacturers. Supply chain complexity can obscure tracking of ingredients’ lineages and identities of parties involved in producing a single supplement. Supply chain complexity and lack of transparency also exists for drugs and is a topic of policy debate,^{22,23} but it is beyond this article’s scope.

With large increases in the number of manufacturers and a subsequent rise in the number and kinds of safety concerns, several companies have engaged independent product certification companies to provide additional security and risk minimization for consumers relying on dietary supplements. For example, companies offer verification

and **certification services** to test whether products contain labeled dose(s) of active ingredient(s) and do not contain microbes, toxins (eg, heavy metals), or substances banned by athletic organizations.^{24,25,26,27,28}

Trends

Not all dietary supplements lack evidence of efficacy. Many products considered dietary supplements are an important part of patient health care, including products to treat vitamin and mineral deficiencies and supplementation during pregnancy. However, as the American Medical Association (AMA) notes: “many products that have medical benefits are commonly overused among the general population in an attempt to improve or maintain health and use in these ways provides little benefit” or even create risks.²⁹ For example, vitamin C is an essential vitamin, antioxidant, and required building block that the human body cannot synthesize. However, ingesting more than the recommended daily allowance of 75 to 90 mg for adults, which is often achieved through diet, may not add additional benefit and can cause unpleasant symptoms such as diarrhea, nausea, abdominal pain, and other gastrointestinal disturbances.³⁰ More generally, studies have noted that dietary supplement use was not associated with mortality benefits in a nationally representative sample of US adults; that supplement use itself does not have direct health benefits; and, in some cases, that excess intake might increase harmful effects, including cancer and mortality.^{24,31} Nevertheless, a recent study found that the majority of patients in the United States are overly optimistic about the results they can achieve through supplementation.³² Physicians would seem to be less optimistic, as only approximately a quarter of dietary supplements are used by adults on the recommendation of their physician.³³

Adulteration

An AMA report describes 2 types of adulteration:

Adulteration of dietary supplements is usually either economic adulteration, when a less expensive ingredient is used in place of a more expensive ingredient listed on the label, or pharmaceutical adulteration, when an active pharmaceutical is included in a product and not listed on the label. Adding to the complexity and safety risks associated with adulteration, pharmaceutical adulteration includes the use of not only FDA-approved drugs, or drugs formerly approved by the FDA and withdrawn, but also drugs used in other countries (and never FDA-approved) and experimental drugs minimally or never tested in humans.²⁹

Based on a literature review,^{20,21,34,35,36,37,38} the AMA report concluded:

Dietary supplements are associated with an estimated 23,000 emergency department visits each year, and many of these visits are due to products that are adulterated with pharmaceutical drugs. The most commonly pharmaceutically adulterated dietary supplements are those marketed as weight loss, sexual enhancement, or sports supplements.²⁹

Responding to Adverse Events

Postmarket surveillance is a key part of identifying safety problems with dietary supplement products. The FD&C Act defines a dietary supplement adverse event (AE) as “any health-related event associated with the use of a dietary supplement that is adverse” (eg, headache, abdominal pain, allergic reaction, rash, or dizziness or lightheadedness).⁷ A serious AE is defined as an AE that “(A) results in—(i) death; (ii) a life-threatening experience; (iii) inpatient hospitalization; (iv) a persistent or significant disability or incapacity or; (v) a congenital anomaly or birth defect; or (B) requires, based on a reasonable medical judgement, a medical or surgical intervention to prevent an outcome described under subparagraph (A).”⁷

Concomitant use of dietary supplements and prescribed medications is common and can result in life-threatening AEs, hospitalizations, and fatalities.³⁹ During the year 2017 to 2018, 57.6% of US adults aged 20 and over reported using a dietary supplement in the past 30 days,⁴⁰ as compared to 69% of US adults aged 40 to 79 who reported using at least one prescription drug and 22% who reported using at least 5 prescription drugs in the past 30 days during the year 2015 to 2016.⁴¹ Additionally, more than two-thirds of older adults concurrently use prescription medications with over-the-counter medications or dietary supplements.⁴² Suspected supplement-related AEs should be reported to the FDA using the Safety Reporting Portal.^{24,43} Reporting by physicians is voluntary but is strongly recommended; the FDA gives extra credence to physician reports, and the voluntary system of passive surveillance is the only opportunity the FDA has to detect harmful dietary supplements.

Although some high-quality studies demonstrate dietary supplements' health benefits, several others show evidence of harm.⁴⁴ Some dietary supplements are known to cause clinically important interactions with drugs.³⁹ Additionally, some dietary supplements have the potential to interfere with laboratory results.⁴⁵ The US Government Accountability Office estimates that a small fraction of the estimated 50 000 AEs each year from dietary supplements are reported to the FDA. Underreporting and the poor quality of information in the few reports submitted make it nearly impossible for the FDA to find and remove supplements that are dangerous.^{46,47}

Patient-Physician Interaction

Physicians or their office staff should include discussion of dietary supplements when reviewing medications with all patients. Risk-based counseling of patients should include discussion of the variable quality of dietary supplements, the **presence of un reputable products** in the marketplace, and which products are commonly adulterated. Physicians should also make an effort to evaluate any potential drug-supplement or supplement-disease interactions based on the products patients are using or considering. Risk-based and open conversation with patients is crucial in minimizing and appropriately identifying interactions.

When counseling patients about dietary supplements, it should be noted that supplementation is not a substitute for a healthful and balanced diet and, in most cases, provides little benefit. Targeted supplementation may be warranted for high-risk populations for whom nutritional requirements may not be met through diet alone, including people at certain life stages and those with specific risk factors.²⁴

Resources exist for patients and physicians who are seeking more information about products, product ingredients, or products with reported violations. The United States Pharmacopeia provides a list of products it has independently verified for quality²⁶; NSF International has a listing of products that are NSF Certified for Sport^{®27}; and the US Anti-Doping Agency hosts a resource for dietary supplement safety education and awareness, Supplement 411.⁴⁸ Other, more comprehensive resources exist but may require a paid subscription. An example is the Natural Medicines database, which claims to contain over 1200 monographs on natural ingredients, including vitamins, herbs, minerals, nonherbal supplements, naturally sourced chemical compounds, and foods; the monographs include information on a variety of topics, including interactions, for both health care professionals and patients.⁴⁹

AMA Policy and Activities

In light of reported information and evidence, the AMA recently updated its already comprehensive policy related to dietary supplements to call for the following²⁹:

- Enhanced FDA resources and enforcement
- Continued research on efficacy, safety, and long-term effects of dietary supplements
- Modernization of DSHEA, including standards for identity, strength, purity, packaging, and labeling and mandating that product listings include safeguards
- Education to improve physicians' capacity to talk with patients about supplements' risks
- “[I]ncrease[d] patient, health care practitioner, and retailer awareness of resources to help patients select quality supplements”
- Education to support label literacy

Conclusion

A safe dietary supplement marketplace will require supply chain transparency and will involve robust AE, drug interaction, and tainted product reporting. Industry self-regulation is insufficient and ineffective for public health protection and patient safety, since unethical individuals and companies manufacture and distribute adulterated, misbranded, and improperly labeled products that pose significant risks. As the dietary supplement industry continues to grow and patients continue to use dietary supplements, revision and modernization of the DSHEA and FDA and Federal Trade Commission oversight of the industry are necessary. Professional and lay education is also needed to help physicians and patients understand this industry and the risks posed by dietary supplements.

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