

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists and pharmacy technicians will be able to:

- Explain what it means to be a "drug"
- Describe the approval processes for prescription and homeopathic drugs and dietary supplements.
- Differentiate a drug and a dietary supplement
- Explain recent regulatory concerns about homeopathic products and supplements
- Describe the role of the pharmacist in helping consumers navigate the differences in FDA oversight among different drug products.



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Law: When is a Medication Not a Drug?

ABSTRACT: A typical pharmacy carries many products, including prescription and OTC drugs, homeopathic products, and dietary supplements. The FDA has jurisdiction over all of these products, but the nature of approval and the degree of oversight differs among them. Prescription drugs are subject to the most rigorous oversight and regulation, but some products do not need pre-market approval. Many consumers and even health professionals have the misconception that all of these products are subject to the same level of control. This continuing education activity will describe the regulation of these products and consider recently proposed regulatory issues and safety concerns.

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DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

What is a drug?

If you asked a pharmacist or pharmacy technician this question, you would probably hear an answer something like "A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." This is, in fact, the U.S. Food and Drug Administration's (FDA) legal definition of a drug.¹

However, it may come as a surprise that another part of the definition is a "substance recognized by an official pharmacopoeia or formulary,"¹ which would expand the definition of "drug" to include homeopathic products. Conversely, the legal description of a dietary supplement specifically excludes it from being defined as a drug. These descriptions affect the regulation and oversight of different substances found in pharmacies.

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Table 1. Comparison of Oversight of Medicinal Products

	Legal Basis	Approved by FDA	Subject to Post-Market Surveillance	Can Make Therapeutic Claim	Subject to GMPs
Conventional (Allopathic) Drugs	FDCA (1938) and Amendments	Yes	Yes	Yes	Yes
Homeopathic Drugs	FDCA (1938) and Amendments	No	Yes	Yes	Yes
Dietary Supplements	DSHEA (1994)	No	Yes	No	Yes

ABBREVIATIONS: DSHEA = Dietary Supplement Health and Education Act; FDA = Food and Drug Administration; FDCA = Food, Drug and Cosmetic Act; GMPs = Good Manufacturing Practices

Pharmacists and technicians are at least generally knowledgeable about the requirement for rigorous testing, including extensive clinical trials and review, before the FDA grants approval for marketing a prescription drug. However, pharmacy staff may be less familiar with oversight of other classes of medicinal substances that are subject to different regulatory guidelines and which, overall, are subject to less stringent requirements than those for prescription products (see [Table 1](#)). Consumers and many health care practitioners are largely unaware of these differences and the degree of oversight the FDA provides² and may look to pharmacy staff to provide guidance.

This continuing education activity will review and contrast the regulation of prescription drugs, homeopathic drugs, and dietary supplements. It will highlight some recently proposed regulatory changes that could impact the promotion and approval of these products.

THE FDA'S ROLE

The FDA is the oldest comprehensive consumer protection agency in the United States federal government.³ Today, the FDA regulates a wide range of consumer products. These include human and veterinary drugs, both prescription and over-the-counter (OTC); foods (except for some meat, poultry and egg products, which are regulated by the U.S. Department of Agriculture); animal food and feed; vaccines and other biologic products, including blood and human tissue; dietary supplements; medical devices intended for human use; radiation-emitting electronic products, such as x-ray machines, microwave ovens, CD-ROMs, and laser pointers; cosmetics (shampoos, face creams and make-up, but not if it meets the regulatory definition of a soap which is regulated by the Consumer Products Safety Commission); and color additives.⁴ Since 2009, the FDA has also regulated cigarettes, smokeless tobacco, and roll-your-own tobacco. In 2016, its authority was expanded to all tobacco products including cigars, e-cigarettes, hookah, and pipe tobacco.⁵ In all, the FDA has regulatory oversight on products accounting for more than \$2.6 trillion spent on consumer goods, representing about 20% of consumer expenditures in the United States.⁶ This includes more than 20,000 prescription drug products.

In the 19th Century, individual states had principal control over domestically produced and distributed foods and drugs; the states were markedly inconsistent in their approaches.⁷ In 1862, the FDA began in the U.S. Department of Agriculture (USDA) as the Division of Chemistry; in 1930, it became the FDA.⁸ It is now part of the U.S. Department of Health and Human Services (HHS).

Enactment of the Food, Drug and Cosmetic Act (FDCA) in 1938 was a watershed event, granting the FDA a mandate for pre-market approval of all new drugs; manufacturers had to prove each drug's safety before marketing it. It also prohibited false therapeutic claims for drugs.⁷ In 1938, Congress enacted statutes giving the FDA jurisdiction to regulate drug labeling and giving jurisdiction to the Federal Trade Commission (FTC) over drug advertising.⁸ (In 1962, an amendment to the FDCA transferred authority for prescription drug advertising to the FDA, but the FTC retained oversight of OTC drug advertising. The FTC also oversees the promotion of OTC supplements.)

Following the FDCA's enactment, the FDA adopted regulations requiring a prescription for any drug for which directions for use would be inadequate for a layperson.⁸ Prior to 1938, the only drugs requiring a prescription were controlled substances subject to the Harrison Act of 1914.⁸ If a drug is safe and effective for self-treatment by the general public without the oversight of a health professional, it may be marketed as an OTC product.⁹ Prescription and OTC drugs must meet different criteria before the FDA approves them for marketing. The FDA was granted the authority to distinguish between prescription and OTC drugs with passage of the Durham-Humphrey Amendment (both sponsors were pharmacists) to the FDCA in 1951. Prior to this amendment, prescription and OTC drugs had no formal distinction and companies often marketed the same drug as both an OTC and a prescription drug. The Amendment established a legal framework to differentiate prescription and non-prescription drugs and authorized the FDA to make the distinction.¹⁰ Prior to 1951, the manufacturer could decide if a drug was going to be marketed as prescription or OTC. The Durham-Humphrey Amendment also prohibited a drug from being marketed as both an OTC and a prescription drug at the same dose and indication. In effect, the differentiation between drug classes is based upon the FDA's determination of the drug's potential toxicity and the degree of supervision needed to



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safely use the drug; the FDA considers both the type of drug and the risks of self-diagnosis by the patient.^{9,10}

Pharmacists and technicians know that one of the FDA's main missions is to assure consumers that drugs and medical devices have been tested and are proven to be safe and effective for their approved and marketed indications.³ Readers seeking a refresher on the prescription drug approval process may look at reference 3.

DRUGS

As noted above, drugs are substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. This is the so-called therapeutic claim, which distinguishes drugs from supplements; only drugs can make this kind of claim.

Homeopathic Products

Homeopathic drugs occupy a special position in the regulatory framework. Unlike dietary supplements, homeopathic products can make a therapeutic claim.¹¹ However, these drugs are not subject to the same level of pre-market scrutiny by the FDA as allopathic drugs.

Homeopathy was established in 1796 and most popular homeopathic medicines have been in the marketplace in the United States for 50 years or more.¹² Homeopathy is considered an alternative medical practice and is generally based on two main principles:

- a substance that causes symptoms in a healthy person can be used in diluted form to treat symptoms and illnesses, a principle known as "like-cures-like," and
- the more diluted the substance, the more potent it is, which is known as the "law of infinitesimals."¹³

Homeopathy is based on the observation that pharmacologically active substances cause symptoms when administered in

large doses to healthy individuals.¹⁴ The theoretical basis for homeopathy holds that when those substances are prepared in very dilute form, they may relieve similar symptoms in conditions resulting from different etiologies. Homeopathic products are used principally for the treatment of symptoms, since the body must first exhibit symptoms before the correct homeopathic drug may be chosen.¹⁴ Homeopathic medicines are rarely used for prophylaxis.¹⁴

The homeopathy industry is small compared to the prescription drug, OTC drug, and dietary supplement industries in terms of revenue, advertising, and the number of marketed products.¹² Although manufacturers have registered more than 7,000 homeopathic medicines with the FDA, it is estimated that only about 1,000 are routinely marketed.¹² Most homeopathic medicines are used to treat cough, cold and flu, muscle pain, and children's ailments, and represent less than 3.5% of all OTC drug products typically found in drugstores.¹² Estimates of homeopathic product sales in the U.S. range from \$1.1 billion to \$1.3 billion annually.¹² In contrast, OTC drug sales are estimated to be more than \$35 billion in 2018¹⁵ while supplements sales topped \$46 billion in 2017.¹⁶

The FDCA officially recognizes drugs and standards published in the Homeopathic Pharmacopeia of the United States (HPUS). Homeopathic drugs are defined as, "any drug labeled as being homeopathic which is listed in the Homeopathic Pharmacopeia of the United States (HPUS), an addendum to it, or its supplements."¹¹ A nongovernmental organization, the Homeopathic Pharmacopoeia Convention of the United States (HPCUS) prepares the HPUS and its members include scientists and clinicians who are trained in the specialty area of homeopathic medicine.¹⁴ HPCUS is a standard-setting organization focusing on the development and publication of general practices and standards for homeopathic products. The HPUS first appeared in 1841 and the current HPUS recognizes 1,286 official homeopathic drug products. The HPUS consists of monographs of individual official homeopathic drugs. The monographs list identifying data

for the drug, and defining specific criteria for manufacturing standards, source, preparation, processing, and quality control.^{14,17} Any drug listed in a HPUS monograph is considered official and requires no further documentation by the manufacturer to be sold.¹⁷ A non-listed drug is considered unofficial and the manufacturer must provide sufficient clinical data to the FDA so it can determine whether the drug is in fact homeopathic.¹⁷

The FDA holds manufacturers accountable for maintaining the same standards of cleanliness, purity, and accuracy as are mandated for other types of drugs, except that the standards are specified in the HPUS rather than the USP.¹⁸ The FDA does not review the self-care claims for homeopathic products but does oversee the language and formats for packaging and labeling. It also inspects manufacturing facilities for adherence to HPUS monographs and quality control procedures.¹⁸ The FDA does not assess homeopathic products' safety or efficacy and there are currently no FDA-approved homeopathic products.¹³

In 1988, the FDA issued a compliance guide ("Conditions Under Which Homeopathic Drugs May be Marketed") describing its enforcement policy on homeopathic products.¹⁹ Under this policy, FDA enforcement actions were, in general, limited to violations of Good Manufacturing Practice (GMP) regulations or labeling requirements.

Recently, the FDA has expressed concerns about some homeopathic products' "significant" risk to patients, noting that there are "misconceptions" that all homeopathic products are highly diluted and composed of "natural" ingredients and, therefore, are incapable of causing harm.²⁰ The FDA withdrew the former guide on October 24, 2019, stating that the guide is "inconsistent" with their "risk-based approach to regulatory and enforcement actions" and issued a revised draft guidance. The FDA noted in its announcement that since homeopathic drugs are not FDA-approved for any use, "they may not meet modern standards for safety, effectiveness, and quality."²⁰ In the announcement accompanying the guide's withdrawal, the FDA specifically cited safety issues with a zinc nasal spray (anosmia from excessive zinc), adverse events from belladonna-containing teething products, and numerous serious GMP violations.²⁰ The FDA has also expressed concern that consumers with serious medical conditions may forgo treatment with conventional approved products that have undergone clinical testing for safety and efficacy. It has warned patients about using homeopathic products intended to treat asthma because they are widely available in retail stores and on the Internet; asthma is a serious condition that if managed improperly, can lead to serious complications.

Homeopathy has many supporters and adherents.^{14,17} However, a 2015 comprehensive assessment of evidence by the Australian government's National Health and Medical Research Council²¹ concluded that "there is no reliable evidence that homeopathy is effective for any health condition." Although some studies



reported that homeopathy was as effective or more effective than another treatment, the studies were rated unreliable because they were of poor quality (not well designed and/or conducted poorly), or they had too few participants to give meaningful results, or both. The report pointed out some challenges such as the difficulty in explaining in scientific terms how a product containing little or no active ingredient can have any effect and confirming that an extremely dilute mixture contains the ingredients listed on the label. Another research challenge is that homeopathic treatments are highly individualized with no uniform prescribing standards for practitioners. The report concluded that homeopathy should not be used to treat health conditions that are chronic, serious, or could become serious. People with these conditions could put their health at risk if they reject or delay more conventional treatments. The report advised people who are considering whether to use homeopathy to first ask for advice from a registered healthcare practitioner and urged consumers to inform their healthcare practitioners about their use.²¹

The FDA listed its anticipated enforcement priorities under the new guidelines²⁰:

- Products with reported safety concerns (e.g., via MedWatch reports)
- Products containing ingredients with potential safety concerns
- Products with routes of administration other than oral or topical
- Products intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions
- Products for vulnerable populations (e.g. infants and children, the elderly, pregnant women, immunocompromised patients)
- Adulterated products.

SUPPLEMENTS

Why is a supplement not considered a drug? Because the law says so.

Supplements are addressed under an entirely distinct federal law, the Dietary Supplement Health and Education Act (DSHEA).²² Enacted in 1994, DSHEA defines and regulates dietary supplements. DSHEA's defines a supplement as a product intended to supplement the diet and that contains one of the following ingredients: "vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of the preceding substances" which are marketed in non-conventional food forms such as tablets, capsules, softgels, gencaps, powders, and liquids.²² Supplements are not drugs, not traditional foods, and not food additives and are regulated differently from them.²³

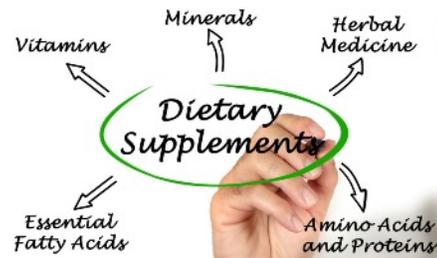
DSHEA emerged in response to a growing interest in the U.S. in supplements. The FDA made many attempts to address regulatory problems with foods and vitamin labels that make health claims. In the early 1990s, prior to the enactments of DSHEA, the FDA sought tougher regulations for dietary supplements, but the agency was unsuccessful.²⁴ Specifically, the FDA wanted to implement a requirement that all health claims made by manufacturers were supported by scientific evidence.²⁵

Congress was concerned that the FDA's oversight was too restrictive of the supplement industry.²⁴ DSHEA's primary goals were twofold: (1) to ensure continued consumer access to a wide variety of dietary supplements; and (2) to provide consumers with more information about the intended use of dietary supplements.²⁶ The law also expanded supplements' definition to include botanical products and it ended the debate over whether supplements should be regulated as drugs or foods.²⁴

Supplement Use

A look at pharmacies' and health food stores' shelves reveals the growth of supplement use in the U.S. Following the passage of the DSHEA, the number of dietary supplement products expanded from 4,000 in 1994 to more than 90,000 by 2014.²³ The Council for Responsible Nutrition, a supplement industry trade group, sponsored a survey in 2019 and found that 77% of adults in the U.S. use supplements, (74% of males and 79% of females).²⁷ The 35 to 54 year-old age group had the highest use (81%) although the gap between age groups was small. Among users, vitamins and minerals were the most commonly used category (76%; multivitamins were the most commonly used product).^{23,28} Thirty-nine percent of consumers reported using herbals and botanicals; 28%, reported using sports nutrition supplements. Other studies have found that 79% of users reported daily use and 10% reported taking five or more supplements daily.²³

Consumers' stated reasons for using dietary supplements are to



maintain or improve overall health and the health of specific organs, prevent disease, increase energy, improve mental health, achieve weight loss, and resolve various health issues such as menopause and hot flashes. Almost 23 million people report using dietary supplements instead of conventional drugs, and 30 million use them instead of OTC medications.²³

A survey conducted in a rural population in Idaho found that almost three of four respondents preferred herbal products to prescription and OTC drugs for treating medical conditions and/or promote overall health.²⁸ Respondents used vitamins most often, followed by fish oil, cranberry, melatonin, glucosamine, cinnamon, and echinacea. Another study identified the most commonly used herbal products in the elderly population as chamomile, echinacea, garlic, ginkgo biloba, ginseng, peppermint, saw palmetto, and St. John's wort.²⁹

Approval

Marketing supplements does not require FDA approval.³⁰ A manufacturer must determine that the dietary supplement it manufactures or distributes is safe. In addition, it must show that any representations or claims it makes about the product are substantiated by adequate evidence to show that they are not false or misleading. The manufacturer does not have to provide the FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products, except in the case of "a new dietary ingredient" (first marketed after October 15, 1994).³⁰ In this case, DSHEA requires that a manufacturer or distributor notify the FDA that it intends to market the dietary supplement in the U.S. at least 75 days before its entry into commerce. It must also demonstrate to FDA why the ingredient is reasonably expected to be safe for use as dietary supplement. There is no authoritative list of dietary

ingredients marketed before the cut-off date and it is the manufacturer's responsibility to determine if the ingredient is "new."^{30,31} Moreover, except for a supplement that contains a new dietary ingredient, manufacturers do not have to register dietary supplements with the FDA before they produce and market them.³¹

As noted above, drugs, but not supplements, can be labeled with therapeutic/disease claims. The FDA defines disease, in part, as "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension)."³² It does, however, exclude diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) from the definition.

Drugs and supplements may both be labeled with non-disease structure-function claims. This type of claim describes the role of a nutrient or dietary ingredient intended to affect the normal structure or function of the human body. For example, "calcium builds strong bones" is an acceptable claim. It may also characterize the means by which a nutrient or dietary ingredient acts to maintain such structure or function. For example, "fiber maintains bowel regularity," or "antioxidants maintain cell integrity" are also acceptable claims. Manufacturers may make claims of general well-being. The distinction between the two types of claims, which may be explicit or implicit, is muddy. The FDA acknowledges that it may not be possible to draw a bright line between them.³² The FDA looks at the context of the statement and provides 10 criteria to assist producers (See **Table 2**). Two characteristics that the FDA examines to help determine if a "condition" will be considered a disease are: (1) if the condition is uncommon; or (2) if the condition can cause significant or permanent harm.³²

Consumers, however, may not appreciate these distinctions. For example, "mild memory loss associated with aging" is a permissible structure/function claim but "Alzheimer's disease or senile dementia in the elderly" is not. Likewise, "helps maintain joint health and flexibility" is permissible but "reduces the pain and stiffness of arthritis" is not. Pharmacists and pharmacy technicians should be vigilant to remind consumers that supplements have not undergone the rigorous clinical testing to demonstrate disease efficacy that is required for drugs.

The labeling of supplements must carry the now-familiar disclaimer: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."³⁰ DSHEA requires this disclaimer whenever a product carries a structure/function claim. The manufacturer is responsible for ensuring claims' accuracy and truthfulness, which are not FDA-approved. DSHEA requires that the disclaimer state that the FDA has not evaluated the claim. The second sentence is required because only a drug can legally claim that it is intended to diagnose, treat, cure or prevent any disease.

Table 2. Permissible v Impermissible Structure-Function Claims for Supplements

What is a Structure-Function Claim?

- (1) Describe the role of a nutrient or dietary ingredient intended to affect normal structure or function in humans ("calcium builds strong bones").
- (2) Characterizes the action by which a nutrient or dietary ingredient maintains such structure or function ("fiber helps maintain digestive regularity");
- (3) Describes a benefit related to a nutrient deficiency disease (like vitamin C and scurvy), as long as the statement also tells how widespread the disease is in the United States.

Criteria:

1. A statement may not explicitly nor implicitly claim that the product has an effect on a specific disease or class of disease.
2. A claim may not refer to a characteristic sign or symptom of a disease or class of disease in terms recognizable to a layperson or health care practitioner.
3. A claim may not present a sign or symptom which is recognizable as an abnormality of the body.
4. A claim may not be disguised as a product name or contain an ingredient regulated by the FDA.
5. A claim may not include a citation to a reference if it refers to a disease use nor use pictures, vignettes, symbols, or other means in a manner that would suggest the presence of a disease condition.
6. A claim may not suggest that the supplement or its ingredients belong to a particular class of drugs or is a substitute for a particular therapy.
7. A claim may not suggest that the product augments a particular therapy.
8. A claim may not suggest that a product treats, prevents, or mitigates adverse events associated with a disease therapy manifested by characteristic signs or symptoms.
9. A statement may not claim that the product has a role in the body's response to a disease or disease vector.
10. The FDA adds a catch-all criterion that prohibits the use of a claim that "otherwise suggests an effect" on a disease or condition.

Source: Reference 32



Other labeling requirements for supplements include the following: a descriptive name of the product stating that it is a supplement; the manufacturer's, packer's, or distributor's name and place of business; a complete ingredient list; the net contents of the product and nutrition labeling in the form of a "Supplement Facts" panel. This label must identify each dietary ingredient contained in the product.³⁰

The FDA also promulgated GMP standards for supplements in 2006,²⁴ but these are less rigorous than the drug standards.¹⁴

PAUSE AND PONDER: How many consumers believe that "natural" is synonymous with "safe"?

Supplement Issues

While there are undoubtedly many beneficial and dependable supplement products, dietary supplements, especially herbals and botanicals, raise unique issues of concern to health care practitioners and their patients. Plant-based products may contain dozens or even hundreds of pharmacologically active compounds, some of which may never have been evaluated for their effects or safety. Many botanical products may report a standardized quantity of an active ingredient on their label, but the constituent responsible for the plant's effects may be unknown.³³

Many factors may also influence the amount and composition of ingredients in the final plant products. These include inherent plant genetic variability, conditions of growth and cultivation (including soil and environmental conditions), the duration and conditions of storage, harvesting, and processing, and manufacturing methods.³³

Supplement products are also susceptible to contamination. An analysis³⁴ found that most supplement products contain detectable levels of toxic agents, including long half-life metals such as lead, cadmium, mercury, arsenic, and aluminum, although only about 10% were above the established daily limits. Pharmaceutical agents also had detectable contamination, but levels were ordinarily very low and none exceeded established limits. The researchers found highest levels of contamination in imported

products from countries with less stringent pollution control.³⁴ An analysis of 40 unique popular single-ingredient herbal dietary supplements sponsored by the Government Accountability Office (GAO) found that nearly half contained organochlorine and organophosphorous pesticides at levels above FDA tolerance limits, and four contained residues from pesticides not registered in the U.S.²⁹ Plant products may absorb toxic compounds from the soil, water, and air. Concentrations may be affected by soil and water conditions, agricultural practices, transportation, substandard processing, and storage conditions. Contaminants may also be deliberately added as fillers.³⁴

Supplements products may also be contaminated with drugs. In an analysis of FDA warnings from 2007 through 2016, pharmaceutical ingredients were identified in 776 dietary supplement products, especially those products marketed for sexual enhancement, weight loss, or muscle building.³⁵ The most commonly identified drugs were sildenafil, sibutramine, and synthetic steroids.

Pharmacists and technicians must recognize another important phenomenon: herb mixtures may contain multiple endogenous ingredients that interact and may alter therapeutic efficacy (see Sidebar, page 8).³⁶ Accordingly, products may differ based upon their composition, especially if the products contain whole plant extracts and isolated ingredients; these may have either a positive or negative effect on activity.³⁶ Interactions have been proposed in products as distinct as Ginkgo biloba and marijuana.³⁶

A lack of standardization is also a concern. In one example, the FDA conducted DNA testing on a selection of top-selling herbal supplements from retail outlets; 79% of these products did not contain any of the herbs listed on their labels.²⁵

PAUSE AND PONDER: As a pharmacist, how confident are you when counseling on supplements? As a technician, how often do you see patients purchase supplements and wonder if they need guidance?

Tech Talk: What is Phytomedicine Component Interaction?

Drugs and supplements that are plant-derived are called phytomedicines. Many people believe that remedies containing whole extracts of plants may be effective because of synergistic interactions between the plant's naturally occurring components. Sometimes, phytomedicines made from whole plants contain more than one ingredient, and when that is the case, the product has additional known or unknown components. Researchers haven't spent much time on this issue until recently. Medical marijuana's growth in popularity has made healthcare providers more aware of this possibility. Research indicates that cannabinoids are the primary source of marijuana's medicinal effects. However, researchers have proposed complex, unique, and synergistic interactions among the different constituents—termed the entourage effect—although the exact nature of these interactions is unclear. And, many phytomedicines and foods contain flavonoids that have assorted functions, and can inhibit enzymes.

Multiple components in phytomedicines can lead to a number of possibilities:

- **Synergism (or an additive effect):** In some instances, plant components may work together with the primary component to increase its activity. Research has demonstrated this is the case with products containing *Artemisia annua*, *Cannabis sativa*, *Ginkgo biloba*, Kava-Kava, and *Piper methysticum*.
- **Protection of unstable constituents:** Whole plant material may contain components like antioxidants that may keep other components from deteriorating or disintegrating. Research has demonstrated this is the case with products containing *Allium sativum*; garlic, ginger, hops, *Humulus lupulus*, valerian, and *Zingiber officinalis*.
- **Independent and unexpected activity:** Some constituents—known or unknown—may be active in their own right, causing desired (good) or undesired (adverse) effects.

Here's the bottom line: Plant extracts are more (or less) than the sum of their individual components. It's difficult for researchers to tease out true relationships between the supposed active ingredients and their effects, separately or together, because such trials are prohibitively costly.

Is there a Dietary Supplement Knowledge Gap?

Research shows that consumers have a number of erroneous beliefs about supplement products.³⁷ Among these are that

- (1) supplements are FDA-approved
- (2) supplements have undergone clinical testing for efficacy and safety
- (3) all supplements are tested for product purity
- (4) manufacturers are required to disclose known adverse effects to consumers.

Research has also found that consumers are more likely to associate dietary supplements with drugs rather than food, and therefore believe that supplements and drugs are similarly regulated.²⁵

In one study,² one-half of adults were unaware that dietary supplements were not FDA-approved and almost two-thirds did not know that supplement advertising undergoes no pre-approval. Another survey³⁸ investigating basic supplement knowledge in adults 60 years old or older found substantial misconceptions. Two-thirds of the participants believed that supplements pose no risk to the general population. In addition, 60% believed that the FDA regulates herbal products and 70% believed that the FDA routinely tests these products. Few participants questioned these products' purity, but nearly half knew that there was a lack of standardization of the contents among different manufacturers.³⁸

A study of 185 undergraduates found that nearly 75% errone-

ously believed that the FDA was responsible for ensuring supplements' safety before sale. Almost 50% believed the FDA analyzes dietary supplements' contents.³⁷ A survey of a nationally representative sample of American adults found that about 50% believed that dietary supplement weight loss aids must be approved by a government agency for safety and efficacy before they can be sold to consumers.³⁷ Furthermore, the legal disclaimer intended to provide transparency to consumers is inadequate and has little to no influence on attitudes about safety and efficacy.³⁷

Health care practitioners also have misconceptions about supplements. One study of 335 attending physicians and residents revealed a low level of knowledge (baseline score of 58%) as measured by a regulatory module.³⁹ About one-third did not know that dietary supplements are not approved before sale to consumers and that there is no requirement for submitting safety and efficacy data before marketing. Moreover, 60% of physicians were unclear on how to report a serious adverse event potentially due to supplement use.

Pharmacists, as drug experts, are available to bridge the knowledge gap. However, a survey of pharmacist knowledge about the therapeutic activity of complementary and alternative medicines (CAM) found a mean correct response of 56%, within the range of earlier studies (43-71%).⁴⁰ Pharmacists may take a small comfort in the finding that they scored slightly higher than health food store employees (who scored a mean of 41%). The authors of this study acknowledged their results demonstrate significant

knowledge deficits among pharmacists.⁴⁰ Only 28% of the surveyed pharmacists expressed confidence in discussing CAM with patients. Unfortunately, technicians were not included in the study.

Despite this lack of adequate knowledge, a large proportion of health food stores recommend dietary supplements for treating a variety of illnesses, from hypertension to cancer.²³ In 2010, the GAO investigated herbal dietary supplement retailers.²⁹ The GAO found that some supplements commonly used by the elderly were questionably or deceptively marketed. In some cases, written sales material claimed that herbal supplements could treat, prevent, or cure conditions such as diabetes, cancer, or cardiovascular disease. In other cases, sales staff told investigators posing as elderly customers that a supplement would prevent or cure high cholesterol or Alzheimer's disease. Investigators were also given potentially harmful medical advice such as taking Gingko biloba with aspirin to improve memory; this combination can increase the risk of bleeding.²⁹

Safety Issues

Supplements can promote public health benefits—such as the potential to provide tangible nutritional, economic, and health advantages—and are generally safe.⁴¹ Although death related to supplements is rare overall,⁴² dangerous side effects can result from supplement consumption. Many supplements have been found to cause serious adverse events.⁴³ The FTC publishes a list for consumers of some of the substances that are associated with more serious adverse events.⁴⁴

A relatively common problem associated with dietary supplement use is severe and sometimes fatal liver injury, particularly when using supplements containing anthraquinones or pyrrolizidines.⁴³ It is estimated that supplements contribute to approximately 15% of cases of drug-induced liver injury and represent the 4th most common cause of injury requiring liver transplantation.⁴⁵ Some supplements are also known to produce kidney damage,^{23,43} and are known carcinogens, hormone modulators, and sympathomimetics.²³ Additional safety issues may arise from megadosing (taking exceptionally large doses); three quarters of Americans believe that supplements can produce greater health benefits if taken at doses above the daily recommended value.²³

Pharmacists also need to be mindful of supplement-drug interactions. Both pharmacokinetic and pharmacodynamic interactions have been documented.^{46,47} Among those with a high risk are Goldenseal (an inhibitor of the major cytochrome drug-metabolizing enzymes CYP2D6 and CYP3A4) and St John's Wort (a potent inducer of CYP3A4 and the efflux transporter p-glycoprotein).⁴⁶ A survey of herbal medicine users uncovered potential adverse herb-drug interactions in 40% of patients, but only 7% of users had observable adverse interactions,

which were generally considered mild.⁴⁸ Health care practitioners who observe an adverse reaction to a dietary supplement or a possible supplement-drug interaction in a patient may report these events to the FDA on-line at MedWatch.⁴⁹ When appropriate, the FDA publishes safety alerts for products, including drugs and supplements. Find recent alerts here:
<https://www.fda.gov/food/recalls-outbreaks-emergencies/alerts-advisories-safety-information>.

Since supplements are widely available without a prescription, patients are not inclined to seek professional guidance prior to purchase and use.²⁸ In one survey, the most commonly reported resource used by consumers to guide their use of dietary supplements is the Internet.²⁸

Under DSHEA, the manufacturer is responsible for ensuring that its dietary supplement products are safe before they are marketed; there is no premarket approval for safety and efficacy as is the case for drugs.³⁰ The manufacturer is not required to conduct tests to assess its safety nor indicate adverse events on its label.⁴¹ Once a product is marketed, the FDA has the burden of proving that a dietary supplement is unsafe before it can take action to restrict the product's use or remove it from the marketplace. That is, the FDA must show that it poses a "significant or unreasonable risk of illness or injury."³⁰

Moreover, the lack of safety must be demonstrated at the serving size, usage conditions, and intended purpose specified on the manufacturer's label, or under ordinary conditions of use if nothing is specified on the label.^{41,24,50} Adverse outcomes occurring from off-label uses cannot be used to demonstrate a lack of safety even if the product is commonly used for these conditions.⁴¹ The FDA may issue an immediate ban, but it must document that the product poses an imminent hazard.^{25,41,50,51}

Some of the difficulties the FDA encounters are illustrated by an action taken against manufacturers of ephedra. Alkaloids of ephedra (Ma Huang and other plants), notably ephedrine, are sympathomimetics with a long history of use.⁵⁰ It gained popularity as a supplement for weight control, energy, and athletic performance.⁵⁰ Prior to its removal from the market, approximately 17% of supplements sold contained ephedra.⁵¹ The FDA began to receive adverse events reports as early as 1993 documenting hypertension, anxiety, insomnia, heart attacks, and strokes.^{24,50} The FDA first proposed a mandatory warning statement in 1997, but it was not enacted.^{24,51} The FDA announced a ban on ephedra in 2003, (effective in April 2004), when it was finally able to achieve the standard necessary to show a significant and unreasonable risk.^{24,50,51} By that time, ephedra was reportedly responsible for 155 deaths.⁵²

In an effort to protect consumers, Congress enacted the Dietary Supplement and Nonprescription Drug Consumer Protection Act in 2006.⁵³ The Act's intent was to enhance the FDA's ability to

identify potential public health issues and respond more rapidly to identified health threats.²⁵ The Act requires manufacturers to submit to the FDA all reports in which their dietary supplement is associated with serious adverse reactions.⁵³ Only adverse events considered serious need to be reported.^{25,53} An adverse effect is considered serious if it “results in death; a life-threatening experience; inpatient hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect.”⁵³ This definition excludes the vast majority of potential adverse effects from the reporting requirement, since most adverse effects will not rise to this level of harm.²⁵ Moreover, there is the likelihood that adverse events are under-reported.²⁵

In 2019, the FDA announced its intention to strengthen regulatory oversight of supplements.⁵⁴ The Commissioner indicated his concern that “changes in the supplement market may have outpaced the evolution of our own policies and our capacity to manage emerging risks.”⁵⁴ The new plan’s main goals are to protect the public through more effective communication about adulterated products on the market, effectively evaluate the safety of dietary supplement products without hindering innovation, and develop new enforcement strategies.⁵⁴ Few details were provided.

At the same time, the FDA stepped up its enforcement activities, sending warning letters and online advisory letters to 17 companies selling supplements that claimed to prevent, treat, or cure Alzheimer’s disease and other medical conditions. They also issued warning letters against companies for illegally selling products as a dietary supplement that contained tianeptine, an unapproved anti-depressant. Some companies made unproven claims that the products could be used to treat opioid addiction.

The FTC has also increased its enforcement efforts to ensure that efficacy claims made for supplements are truthful and supported by competent and reliable scientific evidence.⁵⁶ For example, in October 2019, the FTC reached a settlement with a Florida company whose brochures for its aloe capsules and drink mix contained testimonials from customers. They claimed that the products produced remarkable relief from pain and other ailments with some claiming they no longer needed prescription drugs. Under the settlement, the company faces a financial penalty of \$537,000 and must stop making unsupported health claims.⁵⁷ Similarly, in February 2020, the FTC charged a supplement manufacturer with deceptively promoting an anti-aging product. Its product labeling promised to reverse the aging process, repair damage to the body, and treat diseases by stimulating the production of human growth hormone and stem cells.⁵⁸

Figure 1. Helping Patients Understand the Different Types of Drugs and Supplements

Best

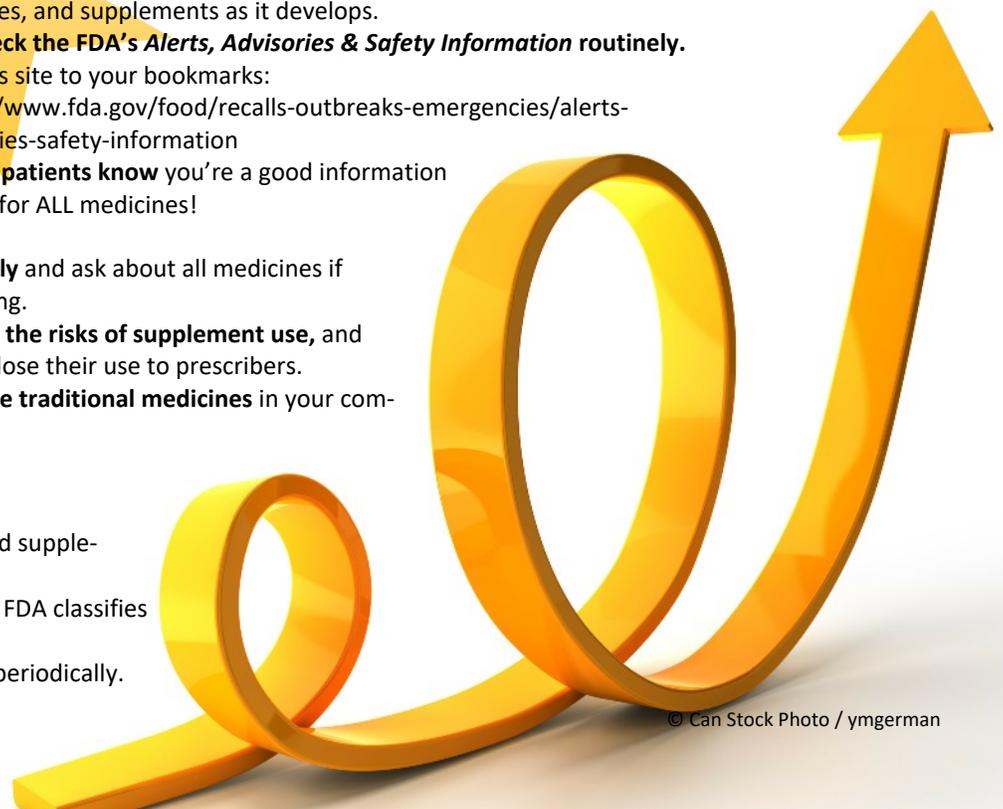
- 1 **Be COMMUNITY CHAMPIONS.** Follow news about drugs, homeopathic remedies, and supplements as it develops.
- 2 **Check the FDA’s Alerts, Advisories & Safety Information routinely.** Add this site to your bookmarks: <https://www.fda.gov/food/recalls-outbreaks-emergencies/alerts-advisories-safety-information>
- 3 **Let patients know** you’re a good information source for ALL medicines!

Better

- 1 **Monitor patients closely** and ask about all medicines if problems may be developing.
- 2 **Educate patients about the risks of supplement use,** and advise them to always disclose their use to prescribers.
- 3 **Identify groups that use traditional medicines** in your community, and be vigilant.

Good

- 1 **Identify buying trends** for OTCs and supplements in your area.
- 2 **Know your inventory** and how the FDA classifies each drug or supplement.
- 3 **Monitor patient’s OTC purchases** periodically. Just take a few minutes and ask!



© Can Stock Photo / ymgerman

The manufacturer further claimed that it could reverse or repair heart attack damage, heart disease, blindness, brain damage from stroke, Alzheimer's disease, Parkinson's disease, deafness, Crohn's disease, and age-related damage to the body's organs, tissues, and joints. The company faced a penalty of \$3.4 million.

SUMMARY AND CONCLUDING COMMENTS

Pharmacists play an important role in providing advice on products available to patients. It is important to be skeptical of product claims and to educate patients about the type and quality of evidence used to support the claims and the degree of oversight required. Patients and even health care providers have misconceptions about these issues, which pharmacists can help remedy. Pharmacists should also take an active role in providing advice about supplement and homeopathic use and safety, just as they would for other OTC products. This is especially important if patients are using products as a substitute for a health care provider's recommendation.

Many consumers do not discuss supplements with their health care practitioners, assuming either that they are adequately regulated by the FDA, they are not "drugs," or "it's natural, so it must be safe." The risk of an adverse effect, interaction, or harm due to discontinuation of conventional products is high. In addition, pharmacy staff needs to stay abreast of potential actions by the FDA and FTC that may change how supplements and homeopathic products are regulated and marketed.

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