NABP
National Association of Boards of Pharmacy

ROGUE RX ACTIVITY REPORT

Risky Dietary Supplements:
How Pharmacists Can Help Protect Patients

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SUMMARY

As the most accessible members of a patient's health care team, pharmacists are well-positioned to counsel patients regarding the risks associated with dietary supplements. While many in the dietary supplement industry comply fully with federal law, some bad actors sell products that are adulterated and/or misbranded in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This report focuses on this subset of dietary supplements, particularly the following: (1) supplements tainted with undeclared active pharmaceutical ingredients (APIs); (2) supplements that contain declared adulterants, such as amphetamine derivatives, steroids, or investigational new drugs; and (3) supplements impermissibly marketed with claims to treat diseases. Of course, there can be overlap between these three categories: a dietary supplement may be misbranded because it is marketed to treat erectile dysfunction; that same supplement may also contain undeclared sildenafil, an adulterant and prescription-only drug ingredient.

Misbranded and adulterated dietary supplements put patients at risk. For example, a cancer patient may forego medically necessary treatment when presented with a supplement that is marketed as a chemotherapy alternative. An adulterated supplement may contain dangerous substances that result in serious adverse health effects. These risks are not merely theoretical. According to researchers, herbal and dietary supplement-induced liver injury now accounts for 20% of hepatotoxicity cases in the United States.[1]

Although regulators work hard to remove adulterated and misbranded dietary supplements from the marketplace, it is a herculean task. Since the mid-1990s, the US dietary supplement market has grown more than tenfold, from a $4 billion industry comprised of about 4,000 products to a $40 billion industry with at least 50,000 products available for sale.[2]

To better protect patients, the National Association of Boards of Pharmacy® (NABP®) supports increased pharmacist education regarding certain high-risk categories of dietary supplements. The Association also encourages pharmacists to proactively counsel patients regarding safety concerns associated with these products and, when informed of adverse events related to dietary supplements, report their concerns to Food and Drug Administration (FDA).

DSHEA Created a Regulatory Framework for Dietary Supplements

The Dietary Supplement Health and Education Act of 1994 (DSHEA) amended the FD&C Act with respect to the regulation of dietary supplements. Under DSHEA, a "dietary supplement" is defined as a product (other than tobacco) intended to supplement the diet that contains one or more of the following "dietary ingredients:" a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by people to supplement the diet by increasing the total dietary intake, a concentrate, metabolite, constituent, or extract.[3]

DSHEA put in place special notification requirements for any company whose dietary supplements contain a new dietary ingredient (NDI), defined as a dietary ingredient not marketed in the US in supplements before the enactment of DSHEA (October 15, 1994).[4] Where a dietary supplement contains an NDI, the manufacturer or distributor must provide FDA with evidence that the NDI is "reasonably expected to be safe."[5] This evidence must be submitted at least 75 days prior to the product's introduction to the market.

Dietary supplements are regulated as a subcategory of food.[6] For this reason, FDA's role in protecting public health begins in earnest after the product enters the marketplace. The agency takes action where a supplement presents a significant health risk or if it is otherwise adulterated or misbranded.*

DSHEA Prohibits the Sale of Adulterated or Misbranded Supplements

Dietary Supplement Companies Are Responsible for Ensuring that Their Products Are Not Adulterated or Misbranded

DSHEA expressly prohibits manufacturers and distributors from marketing adulterated or misbranded dietary supplements. According to FDA, "[t]hat means that these firms are responsible for evaluating the safety and labeling of their products before marketing to ensure that they meet all the requirements of DSHEA and FDA regulations."[7]

A supplement is adulterated if it "bears or contains any poisonous or deleterious substance which may render it injurious to health."[8] A supplement is also considered adulterated if: (1) it contains an

**It is important to note that, although over-the-counter drugs and homeopathic drugs are also sold without a prescription, they have a significantly different regulatory framework than dietary supplements.*

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NDI that has not been noticed to FDA; or (2) the manufacturer or distributor has not submitted adequate evidence that a supplement's NDI is "reasonably expected to be safe."[9] Adulteration is a common problem. Between 2007 and 2020, FDA identified more than 1,000 supplements adulterated with APIs – and the agency only has the resources to test a very small percentage of available products.[10] According to FDA, at least 42 different APIs have been identified in these products, including prescription drug ingredients and their analogues, drugs banned by FDA for safety reasons, controlled substances (CS), and new and untested drug ingredients.[11, 12] Although adulterants are sometimes openly listed on the product label, they are often undeclared. Products with undeclared ingredients are frequently referred to as "tainted."

A dietary supplement is misbranded if its "labeling is false or misleading in any particular."[13] Under federal law, "labeling" is broadly defined to include not only the product's packaging, but also any written, printed, or graphic material that accompanies that product.[14] This includes the manufacturer's or distributer's website, social media, customer testimonials, and affiliate marketing. It even includes a website's meta tags.[15]

Misbranding is a common issue and can occur under different circumstances. For example, a dietary supplement is considered misbranded when the product label lists an ingredient that does not meet the statutory definition of a "dietary ingredient." A supplement is also misbranded when it is impermissibly marketed with claims to diagnose, mitigate, treat, cure, or prevent disease.*, [16]

Certain categories of dietary supplements are more likely to be adulterated and/or misbranded, including those listed on the following pages.

WHAT IS AN ADULTERATED OR MISBRANDED SUPPLEMENT?

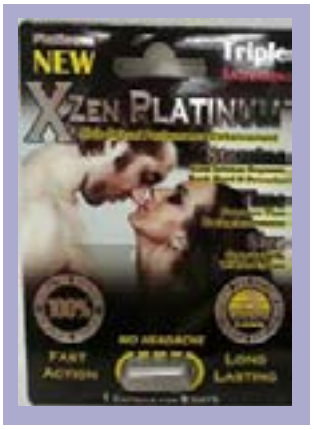
A supplement is **adulterated** if it "bears or contains any poisonous or deleterious substance which may render it injurious to health." It is also considered adulterated if it contains an NDI that has not been noticed to FDA; or the manufacturer or distributor has not submitted adequate evidence that a supplement's NDI is "reasonably expected to be safe."

A dietary supplement is **misbranded** if its "labeling is false or misleading in any particular." Under federal law, "labeling" is broadly defined to include not only the product's packaging, but also any written, printed, or graphic material that accompanies that product.

*There is an exception for a very limited number of claims that are authorized by FDA.

Sexual Enhancement Supplements Often Contain Hidden Drug Ingredients

Between 2007 and 2016, FDA identified 776 dietary supplements tainted with APIs, 353 (45%) of which were marketed for sexual enhancement.[17] These products – frequently sold online – are sometimes tainted with PDE-5 inhibitors, including sildenafil, tadalafil, vardenafil, and their analogues. They have also been found to contain dapoxetine, an unapproved drug in the US that is legally sold in other countries as a prescription-only treatment for premature ejaculation. Products marketed specifically for women have been tainted with flibanserin.



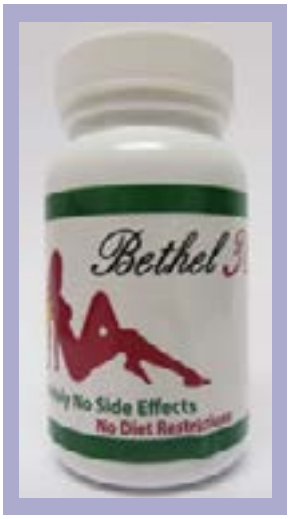
"Xzen Platinum" contained more than 300 milligrams of tadalafil per capsule, which is 280 milligrams more than a maximum dose of Cialis.

These adulterated products have been found to contain dangerously high levels of APIs. For example, a product named "Xzen Platinum" contained more than 300 milligrams of tadalafil per capsule, which is 280 milligrams more than a maximum dose of Cialis.[18]
Another product, named "Mojo Nights," contained undeclared tadalafil, sildenafil, sulfoaildenafil, sulfosildenafil, and hydroxythiohomosildenafil.[19] Like Xzen Platinum, many of these tainted sexual enhancement products are sold in single or limited dose packaging.

Weight Loss Supplements Are at Higher Risk of Adulteration and/or Misbranding

Dietary supplements marketed to aid in weight loss are also at higher risk for adulteration and/or misbranding. Most commonly, tainted weight loss supplements are found to contain undeclared sibutramine, a Schedule IV CS that was previously approved under the brand name Meridia.[20] This product was recalled from the US market in 2010 due to an increased risk of major adverse cardiovascular events.[21]

Phenolphthalein – an over-the-counter laxative that was recalled because of potential carcinogenic effects – is another common undeclared weight loss supplement adulterant.[22] Sometimes, tainted products contain both sibutramine and phenolphthalein. Like their sexual enhancement



"Bethel 30" was found to contain 84.2 milligrams of sibutramine and 88.9 milligrams of phenolphthalein per capsule.

counterparts, tainted weight loss products can contain dangerous levels of APIs. For example, a product named "Bethel 30" was found to contain 84.2 milligrams of sibutramine and 88.9 milligrams of phenolphthalein per capsule.[23] Other undeclared APIs found in weight loss products include fenproporex, bumetanide, furosemide, phenytoin, rimonabant, cetilistat, lorcaserin, and fluoxetine.[24]

R-beta-methylphenethylamine (also known as BMPEA) is another common weight loss supplement ingredient (although, unlike sibutramine and phenolphthalein, BMPEA is typically included on the product label). Because BMPEA is a synthetic stimulant, it does not meet the definition of a "dietary ingredient" under the FD&C Act; therefore, dietary supplements labeled as containing BMPEA are considered misbranded. Some manufacturers claim that BMPEA is found naturally in the plant species *Acacia rigidula* and label their products as containing this botanical ingredient; however, FDA disputes this finding and asserts that, regardless, *Acacia rigidula* is an NDI that does not meet the requirements to be lawfully marketed in the US.[25]

Dietary Supplements Marketed to Boost Athletic Performance May Contain Unlawful Stimulants

Some manufacturers of athletic performance supplements openly include ingredients that either: (1) do not qualify as "dietary ingredients," as defined in the FD&C Act; or (2) are considered NDIs, which lack sufficient evidence of safety. As noted above, products containing these types of ingredients are considered adulterated and/or misbranded.

Manufacturers of "energy boosters" or "pre-workout" supplements sometimes add synthetic stimulants to their products. For example, 1,3-dimethylamylamine (known as DMAA and methylhexanamine) is an amphetamine-like substance found in some "pre-workout" supplements. To avoid regulatory scrutiny, unscrupulous manufacturers sometimes market DMAA as "geranium oil" or "geranium extract." However, FDA has stated that it is "not aware of any reliable science indicating that DMAA exists naturally in plants."[26] DMAA has been associated with a number of adverse events, including heart attacks and the deaths of two US soldiers.[27]

Other unlawful stimulants commonly found in workout boosters include DMBA (an analogue of DMAA that is also known as 1,3-dimethylbutylamine and AMP citrate); DMHA (also known as 1,5-dimethylhexylamine and octodrine); and methylsynephrine (also known as oxilofrine). In addition to their prohibition under the FD&C Act, all four substances mentioned above are prohibited for use in sport by the World Anti-Doping Agency.[28]

Dietary Supplements Marketed as Cognitive Enhancers Sometimes Contain Foreign Drugs and Investigational New Drugs

Dietary supplements marketed as "cognitive enhancers" or "nootropics" are increasingly popular.* Some of these products contain unapproved drug ingredients. For example, picamilon, phenibut, and piracetam are well-known "nootropic" supplement ingredients that do not qualify as "dietary ingredients" under the FD&C Act.

Picamilon and picamilon are approved drugs in the Russian Federation that are used to treat a variety of neurological conditions.[29,30] Piracetam is an investigational new drug for which substantial clinical investigations have been made public in the US. Because there is no evidence that piracetam was marketed as a dietary supplement or a food prior to the authorization to investigate piracetam as a new drug, piracetam cannot legally be included in dietary supplements.[31]

Some Bodybuilding Supplements Contain Steroid-Like Ingredients

Selective androgen receptor modulators (SARMs) are a class of androgen receptor ligands that are impermissibly included in bodybuilding supplements. FDA has announced that SARMs are "unapproved drugs" that are associated with serious safety concerns, including liver damage and increased risk of heart attack and stroke.[32] Common SARMs include: enobosarm (also known as Ostarine and MK-2866); ligandrol (also known as LGD-4033); and Andarine (also known as GTx-007 and S-4). In November 2019, Senator Chuck Grassley introduced the SARMs Control Act of 2019, which (if passed) would add SARMs to Schedule III of the Controlled Substances Act.[33]

Pure or Highly Concentrated Caffeine Supplements, Sold in Bulk or Liquid Form, Are Illegal

Powdered or liquid highly concentrated caffeine, sold in bulk and marketed as a dietary supplement, has been linked to at least two deaths in the US in the past several years.[34] According to FDA, the difference between a safe amount and a life-threatening amount of caffeine in highly concentrated products is nearly impossible to measure with standard kitchen measuring tools.[35] For example, a single teaspoon of pure powdered caffeine is equivalent to the amount of caffeine in 28 cups of coffee.[36]

In 2018, FDA issued a "guidance for industry" document regarding pure or highly concentrated caffeine. In the document, FDA states, "in general we consider products containing potentially lethal amounts of pure or highly concentrated powdered caffeine, sold in bulk such that the

**"Nootropic" is an industry term that is used to describe an ingestible product that enhances cognitive function. "Nootropics" are sometimes referred to as "smart drugs."*

consumer is required to separate out a safe serving from a potentially lethal amount, to meet the standard for adulteration under section 402(f)(1)(A) of the [FD&C Act]."[37] FDA is also taking active steps to remove these types of products from the marketplace. Since 2016, the agency has issued nine warning letters to manufacturers and distributors of powdered and liquid highly concentrated caffeine supplements.[38]

Dietary Supplements Are Misbranded When Marketed with Claims to Diagnose, Mitigate, Treat, Cure, or Prevent Disease

Dietary supplements that are marketed to treat diseases are also risky, since patients may forego medically necessary treatments in favor of these products. Because dietary supplements cannot be legally marketed with claims to treat or prevent disease – unless those claims have undergone pre-market review by FDA and have been authorized or approved – any dietary supplement that makes such claims is misbranded under the FD&C Act.

What constitutes a "disease" under federal law? FDA defines "disease" as "damage to an organ, part, structure, or system of the body such that it does not function properly […] or a state of health leading to such dysfunctioning […]; except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition."[39] This definition is interpreted broadly by FDA, since disease claims may be either express or implied.

FDA Enforcement

To address the problem of adulterated and misbranded dietary supplements, FDA has a number of enforcement options at its disposal. The agency can publish import alerts, issue warning letters, and facilitate recalls. In extreme circumstances, FDA can pursue a regulatory ban on an ingredient. Where appropriate, the agency also works with the Department of Justice (DOJ) and other federal agencies to pursue criminal penalties.

Import alerts are issued when FDA has enough evidence to allow for "detention without physical examination" of products that appear to be in violation of FDA's laws and regulations.[40] These alerts shift the burden to the importer to ensure that its products comply with US law. If an importer's products are detained, the importer can present evidence to FDA to support release of its products from detention.

The agency also regularly issues warning letters to manufacturers and distributors of risky supplements.[41] Indeed, FDA has issued hundreds of warning letters to dietary supplement companies that market products with claims to treat, prevent, cure, or mitigate diseases. Because of limited resources, the agency prioritizes supplements marketed to treat serious diseases such as cancer, Alzheimer's, HIV/AIDS, autism spectrum disorders, and opioid addiction. When sending out warning letters, FDA sometimes partners with the Federal Trade Commission (FTC). For example, FDA and FTC have issued over 110 joint warning letters to companies that market products, including dietary supplements, to prevent and treat coronavirus disease 2019 (COVID-19).[42]

Under the Food Safety Modernization Act, FDA has the power to issue a mandatory recall for a dietary supplement if there is a reasonable probability that the product is adulterated or misbranded, and it could cause serious illness or death.[43] However, FDA must give the responsible party an opportunity to conduct a voluntary recall before ordering a mandatory recall.[44] For this reason, when FDA discovers that a dietary supplement is tainted, it almost always oversees a "Class I" voluntary recall. For example, in February 2020, FDA published a voluntary nationwide recall of all lots of Up2 and Bow & Arrow, two sexual enhancement supplements that were found to contain undeclared sildenafil.[45]

FDA can also ban ingredients via administrative rulemaking. To date, the agency has banned only one dietary supplement ingredient: ephedrine alkaloids. These substances – prevalent in certain species of Ephedra – were commonly included in weight loss supplements in the 1990s and early 2000s and were found to have a significant risk profile.[46]

In some cases, FDA's Office of Criminal Investigations partners with the DOJ and other federal agencies to pursue criminal penalties against individuals and companies that market adulterated and/or misbranded dietary supplements. For example, in 2019, the DOJ entered a plea agreement related to the illegal importation and sale of $11 million worth of tainted sexual enhancement supplements. According to the complaint, from 2011 through early 2017, one of the defendants illegally imported shipments of powdered tadalafil from suppliers in China and then manufactured the drug into at least 5.5 million pills that were marketed as dietary supplements. To boost sales, the defendant made the pills with up to 14 times the level of tadalafil found in Cialis. After FDA issued public notifications that the pills were tainted, the defendant relabeled the tainted products and continued selling the products under new names.[47]

To provide information to stakeholders and consumers, FDA issues press releases and alerts. The agency also regularly adds supplements to a tainted dietary supplement database.[48] In 2019, FDA began taking a more proactive approach to potential supplement adulterants: the agency created the "Dietary Supplement Ingredient Advisory List." The list is intended to quickly notify the public when, following a preliminary investigation, FDA identifies ingredients that do not appear to be lawfully included in dietary supplements.[49] The list currently includes ten common dietary supplement ingredients (eg, higenamine, hordenine, and sulbutiamine).

A final comment regarding enforcement: Although this report focuses on FDA regulations and enforcement, other federal and state agencies also work to remove risky dietary supplements from the market. For example, FTC regularly files cases against supplement companies that violate its truth-in-advertising law. In addition, FTC frequently seeks injunctive relief, restitution, and consumer refunds. As noted above, FTC also issues warning letters, alone and in conjunction with FDA. State attorneys general sometimes use state consumer protection laws to pursue violative dietary supplement companies. For example, in 2015, the Oregon Attorney General filed a lawsuit against a major supplement retailer, claiming that it violated the Oregon Unlawful Trade Practices Act by misrepresenting certain products as lawful dietary supplements when they illegally contained picamilon and BMPEA.[50]

Conclusion

According to a 2019 study by The Pew Charitable Trusts, 70% of Americans had used dietary supplements in the previous two years.[51] Unfortunately, more than half of supplement users mistakenly believe that, prior to sale: (1) FDA tests supplements for safety; or (2) manufacturers are required to submit proof of product safety to FDA.[52] This could not be farther from the truth. One US study estimates that each year 23,000 emergency department visits and 2,000 hospitalizations are attributed to adverse events related to dietary supplements.[53]

Because of the discrepancy between consumer knowledge and potential risk, pharmacists play a critical role in protecting patients from unsafe supplements. For this reason, NABP supports increased pharmacist education about misbranded and adulterated dietary supplements. The Association also encourages pharmacists to proactively counsel patients regarding safety

concerns associated with these products and, when informed of adverse events related to dietary supplements, report these events to FDA by either submitting a report through the agency's Safety Reporting Portal or by calling FDA's hotline.[54]

For information about NABP's Rogue Rx: Activity Report, or the Association's research and reporting capabilities, please contact Associate Executive Director of Professional Affairs, Melissa Madigan, via email at mmadigan@nabp.pharmacy.

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