Perspective

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Breaking the gridlock: Regulation of dietary supplements in the United States

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Abstract

Despite increasing use of dietary supplements by millions of consumers, regulation of these products has not kept pace with changes and risks in the market. A major reason for this policy gridlock is the inability of different parties to come to an agreement on a path forward. The purpose of this paper is to set out a new framework for regulation in which consumers, industry, and regulators can all find common ground. This framework is based on a conceptual shift from 'benefit versus risk', the model for prescription drugs, to 'access with safety'. Steps should include registration of all dietary supplements to permit easier enforcement against rogue products, a stronger disclaimer explaining the limited role of FDA in evaluating structure/function product claims, the establishment of standard laboratory techniques for characterization of products, and more clear authority for the agency when safety concerns arise.

Introduction

An estimated one hundred million Americans purchase dietary supplements each year.[1] These include such therapies as iron for iron-deficiency anemia, Vitamin D for rickets, and calcium supplementation for osteoporosis. Many consumers take dietary supplements to assure an adequate intake of vitamins and minerals and to gain health benefits from herbal extracts. Yet more than 20 years after the passage of major legislation on dietary supplements, substantial sections of the market for these products remain disorganized, deceptive, and dangerous.

Hundreds of products marketed as supplements have been spiked with illicit pharmaceuticals, risking serious injury and death.[2] In the first three months of 2015 alone, the US Food and Drug Administration (FDA) warned about or recalled over 30 tainted sexual enhancement products including *Libigrow*,[3] *Rhino Blitz Gold 3000*,[4] *Stiff Nights*,[5] and *Vigra*[6] for containing prescription erectile-dysfunction drugs sildenafil (*Viagra*), tadalafil (*Cialis*), or a related pharmaceutical analogue. In 2014, FDA recalled *Magic Slim*,[7] *SLIM-K*,[8] *Super Fat Burner*,[9] and *Forever Beautiful*[10] for containing the weight-loss drug sibutramine (*Meridia*) and the laxative phenolphthalein; both of which are regarded as unsafe pharmaceuticals by FDA and have been withdrawn from the US market. Among sports supplements, *Mayhem*[11] was recalled for containing the steroid dexamethasone (*Decadron*) and antihistamine cyproheptadine (*Periactin*), while Wyked Labs *Swoll-250* contained anabolic steroids.[12] *Doctor's Best Red Yeast Rice*, sold as heart healthy, was found to contain lovastatin (*Mevacor*)[13] and *Pro ArthMax* to contain chlorzoxazone (*Lorzone*), nefopam (*Acupan*), diclofenac (*Voltaren*), ibuprofen (*Motrin* and *Advil*), naproxen (*Aleve*), and indomethacin (*Indocin*).[14] Recalls may have little effect on the availability of spiked products.[15] Even with support among dietary supplement trade organizations for greater enforcement,[16] a recent study found dozens of recalled supplements were still available for purchase, two-thirds containing banned ingredients.[17]

Beyond the types of claims for dietary supplements permitted under law, manufacturers and sellers of dietary supplements frequently make unproven and unauthorized claims that their products prevent, treat, or cure disease. In recent years, the FDA has cited manufacturers of hundreds of products for promising relief from a wide variety of conditions including diabetes, heart disease, HIV/AIDS and cancer.[2, 18-22] A 2003 review of claims made on 273 websites selling dietary supplements found that 55% of sites made unauthorized and illegal claims to treat, prevent, diagnose, or cure specific disease.[23] The Government Accountability Office found that one in five dietary supplements sold for weight loss or immune system support included prohibited disease-related claims on their labels.[20] Such claims not only mislead consumers into buying the advertised products, subjecting them to unknown risk with no clear evidence of efficacy, but can also lead consumers not to seek treatment proven to be safe and effective.

There is poor compliance with manufacturing standards for dietary supplements. For more than 15 000 domestic and international manufacturers of dietary supplements sold in the United States,[24] the FDA conducts just 400 inspections. The agency finds significant deficiencies in about two-thirds of all the inspections it conducts, with most facilities cited for multiple, serious violations.[24] Commonly identified problems include failure to verify that a finished batch of dietary supplements meets product specifications such as identity, purity, strength, and composition; failure to verify the identity of a dietary ingredient prior to use through at least one appropriate test or examination; and failure to establish and/or follow written procedures for quality control operations.[25, 24]

Consumers have reason to wonder whether the ingredients listed on a package of dietary supplements match what is in the product. Certain segments of the herbal-supplement market practice so-called economic adulteration, substituting a less-expensive for a more-expensive ingredient, including cheap fillers and related substitute species.[26] Investigators have found powdered rice and laxatives in place of St John's Wort,[27] black walnut in place of Ginkgo biloba,[27] and various species of Asian actae in place of black cohosh.[26, 28] Other studies have found only trace

amounts of the advertised ingredient present in the products.[29] While the dietary supplement industry has questioned the validity of the methods used in some of these studies, the industry has not been able to demonstrate a greater level of product fidelity using alternative approaches.[30] On 30 March, 2015, the retailer GNC promised to implement new reporting systems; phase in the use of advanced DNA testing to authenticate all of the plant species used in its store-brand herbal supplements; and extensively test for undisclosed common allergens in products such as tree nuts, soy, and wheat.[31] Other industry groups, such as the American Herbal Product Association, are considering authentication programmes that would utilize basic microscopy, high-performance thin-layer chromatography, and ultra-performance liquid chromatography.[32]

Gaps in oversight of new ingredients in dietary supplements are raising serious safety concerns. Some industry observers have questioned the manufacturers' compliance with the requirement that the FDA be notified of ingredients not present prior to 1994; in the first 20 years of the requirement, the FDA received only several hundred notifications of new dietary ingredients, despite more than 55 000 dietary supplement products on the market.[33, 34] Recently, the FDA has required the withdrawal of several products on safety grounds. One of these, *OxyElite Pro*, resulted in more than 90 cases of severe liver injury and one death before it was withdrawn from the market.[35, 36] More recently, a potentially dangerous amphetamine isomer, BMPEA, has been identified in numerous sports nutrition and weight loss products.[37-39] In 2013, the Government Accountability Office found substantial underreporting of adverse events for dietary supplements, with only about 1 in 50 complications reaching the attention of the FDA.[40]

Broken promises

This is not the regulatory system for dietary supplements sold to the American public. In 1994, Congress passed, and President Clinton signed, the Dietary Supplement Health Education Act. The law addressed ongoing disputes over the regulatory framework for dietary supplements. It established the legal basis for permissible claims and provided the basis for manufacturing inspections, with no provision for premarket review for safety or effectiveness. In signing this legislation, President Clinton stated:

> After several years of intense efforts, manufacturers, experts in nutrition, and legislators-- acting in a conscientious alliance with consumers at the grassroots level-- have moved successfully to bring common sense to the treatment of dietary supplements under regulation and law.[41]

Since the law's passage, and particularly over the last decade, additions to the framework in DSHEA have sought to improve oversight of dietary supplements. However, these statutes also failed to live up to their promise.

In 2006, following the release of a report on evaluating safety of dietary supplements by the Institute of Medicine,[42] Congress passed the Dietary Supplement and Nonprescription Drug Consumer Protections Act. The law required manufacturers to report serious adverse events related to dietary supplements. At the time Senator Richard Durbin said, 'With this bill, the FDA will have the tools to monitor supplements that cause dangerous health problems like heart attack, stroke, seizures and liver failure.'[43] Michael McGuffin, President of the American Herbal Products Association, stated that the legislation would demonstrate that 'Dietary supplements as a class have a remarkable safety record.'[44]

In 2007, the FDA released regulations establishing standards for current Good Manufacturing Practices (GMPs) for dietary supplements. At the time, FDA Commissioner Andrew C. von Eschenbach stated the regulations would '[help] to ensure the quality of dietary supplements so that consumers [could] be confident that the products they purchase contain[ed] what is on the label'.[45] Steve Mister, President and CEO of Council for Responsible Nutrition, stated:

> We are optimistic that these new dietary supplement GMPs will enhance consumer confidence in these popular products by raising the bar on production standards, helping ensure quality, and leveling the playing field for all dietary supplement companies.[46]

Utah Senator Orrin Hatch stated, 'GMPs are crucial because they assure the public that the products they are buying live up to their labels.'[47]

In 2011, the FDA released draft guidance that clarified what constituted a new dietary ingredient requiring additional assurances of safety and streamlined the necessary reporting structure. The agency's press release called measure a 'preventive control to ensure that consumers are not exposed to unnecessary public health risks from new ingredients with unknown safety profiles'[48]

Yet again, such assurance was not forthcoming. There are several perspectives on why.

Some argue that ongoing problems in the regulation of dietary supplements have their root in the underlying DSHEA law, with critics pointing to three major gaps.

First, DSHEA does not require registration of products, either before or after marketing. As a result, FDA does not know what is in the market at any point in time, and manufacturers can reformulate products under existing brand names. For example, USP Labs has reformulated its workout supplement, *OxyElite* and *Jack3d*, multiple times under the same and different names following the association of particular products with serious adverse events including death.[49, 50] In this case, these reformulations did not make the products safer; in fact, the rebranded product in question also led to serious injury and death.[51]

Second, DSHEA creates a high bar for the FDA to demonstrate a safety problem prior to regulatory action. In the case of Ephedra, it took the agency nearly a decade in the setting of thousands of reported adverse events before pulling the ingredient from the market.[52, 53] Following the agency action, Dr Ronald Davis of the American Medical Association testified that the Ephedra case demonstrated 'that the Dietary Supplement Health and Education Act of 1994, or DSHEA, fails to provide for adequate Food and Drug Administration oversight of dietary supplements'.[52]

Third, DSHEA critics have noted that the law does not require a premarket review of safety or efficacy, as is required for pharmaceuticals and high-risk medical devices. As a result, a company can design, develop, manufacture, and sell a product without meaningful external review. Senator Richard Durbin bluntly stated that in the absence of such review, the American consumer is 'playing the role of the rat in the laboratory, the guinea pig'.[54]

Others have pointed to numerous technical challenges implementing DSHEA. For example, while pharmaceutical adulteration is illegal under DSHEA, the law requires the FDA to identify the chemical tainting of a product before taking enforcement action. This can be a complicated laboratory challenge, with each analogue of a prescription drug requiring its own chemical analysis. The use of analogues is especially frequent in dietary supplements claiming to spur sexual enhancement or treat erectile dysfunction.[55, 56] Manufacturers of these products often alter existing pharmaceuticals by simple chemical variations in order to evade detection. The FDA must then conduct a wide range of laboratory techniques to identify the adulterated ingredient, including nuclear magnetic resonance, high resolution microscopy, liquid chromatography-mass spectrometry, ultraviolet and infrared spectroscopy analysis.[57] By the time there is evidence for enforcement, the product could have disappeared from the market, only to reappear in another form.

Still others have found fault with FDA funding and enforcement of existing provisions of law. This has been a common complaint of the supplement industry. In 2013, a spokesperson for the Council for Responsible Nutrition stated the, 'FDA needs to be a lot more aggressive in the enforcement stage because if they do that, it will send a message to the other companies'.[58] The United Natural Products Alliance has said that 'the answer [to this problem] is to not add additional paperwork and cost for both the agency and reputable dietary supplement companies, but for Congress to fully fund FDA to exercise the power it already has to speed up enforcement of key regulations, such as good manufacturing process.'[59]

Over the last 21 years, the agency has cited hundreds of products for violating the law, but has only sought injunctions or criminal prosecutions against a small subset of them. From 2002 to 2008, the FDA and the Department of Justice only successfully criminally prosecuted 14 companies.[60, 61] While the agency has cited hundreds of companies for violating manufacturing practices each year,[62] it has sought to permanently remove authority to market from just two of them, the first large case being in 2011, 17 years after the FDA had this authority.[60, 63] While additional resources would facilitate additional prosecutions, the rigidness of the DSHEA framework significantly limits the FDA's ability to move quickly against many potential targets at once.

A path forward

Despite calls for change from many quarters, including industry, there has been little progress in the regulation of dietary supplements. This policy gridlock may seem surprising in light of what appears to be broad agreement on the need to rid the market of tainted and dangerous products. Yet public discussion about the safety of dietary supplements has masked deep disagreement over how to regulate manufacturers' claims about their products. It is this disagreement that has posed a major roadblock to progress.

Many health professionals believe that dietary supplements should be regulated for efficacy in the same manner as pharmaceuticals, with the requirement that supplement manufacturers demonstrate that a product's benefit outweighs the risk. For example, the American Medical Association has repeatedly called for Congress to modify DSHEA to require 'that dietary supplements and herbal remedies, including those products already in the marketplace, undergo FDA approval for evidence of safety and efficacy'.[64] The American Society of Health-System Pharmacists has taken the position that in the absence of safety and efficacy the use of dietary supplements 'presents substantial risks to public health'.[65]

On the other side, manufacturers are highly resistant to additional evidence requirements on efficacy. For example, the Alliance for Natural Health has asserted that that 'The vast majority of supplement health claims have *plenty* of scientific basis – just not the random-controlled trials (RCT) that…FDA want[s].'[66]

Consumers of dietary supplements have long cared far more about FDA oversight of safety than efficacy. As Swann's fascinating history in this journal makes clear, popular pressure on the FDA to permit sales and claims for dietary supplements spanned the entire twentieth century.[67] While some Americans believe that the FDA does review supplements for efficacy,[68] a recent survey found that more than only 25% of supplement users 'responded that they would cease their use of a supplement if public health authorities stated it was ineffective'[69] These results were consistent with a 2001 study that found more than two-thirds of users would still take their favourite dietary supplement even if the FDA found it to be ineffective. But this resistance to the government's perspective did not extend to safety. Four in five supported allowing the government to 'remove dietary supplements from the market if FDA shows that they are unsafe'.[70]

DSHEA reflected an uneasy compromise on efficacy. The law permitted nutrient claims, health claims, and structure function claims with varying conditions, but prohibited claims on the prevention and treatment of disease. Nor did the law did provide the FDA with the authority to approve products prior to marketing, or even to require the submission of data justifying a claim related to the structure or function of the human body. This framework has created tension between the FDA and industry over the potential value of supplements to consumers.

Ongoing conflict over efficacy regulation is reflected in current policy debates. Senators Richard Durbin and Richard Blumenthal have proposed legislation that would give the FDA the 'authority to require manufacturers to provide proof for any potential health benefit claims'.[71] Industry trade groups objected strongly to this provision, calling the legislation a 'non-starter'.[72] The Council for Responsible Nutrition stated: 'We share Sen. Durbin's concern that consumers should be able to expect dietary supplements are safe and beneficial, but adding new layers of bureaucratic mandates is a shotgun approach when we need FDA to take a rifle-like aim at companies that are putting consumers at risk.'[73]

There are two approaches to addressing claims for the efficacy of dietary supplements. One would be to find a new approach to assessment of claims, either at the federal or state levels. The New York Health Commissioner, for example, recently formed a task force that recommended the creation of a state level registry of manufacturers and distributors among others to ensure the safety and efficacy of all supplements.[74]

However, there are three principal challenges to the adoption of new review standards for efficacy. First, it is difficult, if not impossible, to imagine a political consensus forming on the need for such standards. This is in part because the perspective and interests of various parties are in direct conflict; manufacturers support a weakening of standards while medical professional groups would like to see them strengthened. It is also in part because the public may push back at the perception that certain trusted products may not be available. Second, given the volume of supplements and formulations in the market, review of evidence of efficacy on an industry-wide scale is a staggering administrative challenge. Third, it is difficult to justify why there should be strict review of benefit and risk for supplements, in the absence of such review for many over-the-counter medications, homeopathic remedies, and other products not intended to prevent or treat disease.

An alternative approach would be for policymakers to defer conflict over efficacy and instead embrace the goal of promoting access to safe dietary supplements. Under this approach, FDA oversight would explicitly shift from 'benefit versus risk' to 'access with safety'. Instead of a broad review of claims by the FDA, new legislation would prioritize stronger oversight of identity of supplements and risk to consumers.

We suggest that this new approach proceed in three phases. The first phase would include two basic elements: a requirement for manufacturers to register each dietary supplement product with the FDA and greater authority for the FDA to extend disclaimers so that the public better understands the nature of the agency's oversight. It is now generally recognized that the FDA cannot effectively oversee the safety of a market with a history of thousands of potentially dangerous products without knowing what is supposed to be for sale. Registration of each unique product would allow the agency to quickly identify non-registered products and order them off the market, without the need for time-consuming laboratory analysis. The FDA could also keep individuals with histories of serious regulatory violations from registering additional products for specified periods of time. It could also permit a significant amount of industry self-regulation: If each product package were required to provide a Quick Response (QR) code that linked to a valid FDA registration, then wholesalers, retailers, and others could quickly check to be sure the product was registered before offering it for sale. Registration is an idea that has support in the supplement industry, with one leader noting it would provide the FDA a 'faster, easier way to say they're not in compliance'.[75]

At the same time, stronger disclaimers would provide reassurance to industry that the FDA is not moving towards greater regulation of efficacy and would help address the findings of a recent analysis of studies that 'found that consumers were generally unaware of the disclaimer or attached no weight to it in their perceptions of the product'.[76] The effectiveness of disclaimers should be routinely tested in diverse populations of consumers.

A second phase would include two more steps. First, to provide greater assurance of product identity to consumers, the FDA would establish standard manufacturing procedures for botanicals accompanied by a standard laboratory technique to characterize each product sold. This would avoid the emerging problem that manufacturers, retailers, and law enforcement officials may use differing and possibly conflicting standards. Moreover, a reliable laboratory method that characterizes a supplement would make manipulation and adulteration far more difficult.

The search for a consistent method to identify dietary supplements might start with work underway by the United States Pharmacopoeia (USP). The USP has laboratory standards for the production of herbal supplements. If such standards were adopted for manufacturing, the USP might extend this work into a set of analyses that could be sent to the FDA with registration. Such a submission might help the agency to catch significant changes in the product's composition, should concerns arise.

Second, to protect consumers from unreasonable safety risks, the FDA would strengthen surveillance of potential adverse effects,[77] with authority to suspend sales during an agency review in a setting of sufficient concern, and remove ingredients from the market based on the standard recommended by the Institute of Medicine: 'the appropriate scientific standard to be used to overturn [the] basic assumption of safety is to demonstrate significant or unreasonable risk, not *prove* that an ingredient is unsafe'.[42] For new ingredients, based on their chemical structure and safety record, the FDA should have the ability to trigger a safety review prior to marketing. While not as stringent as the European system, where all new ingredients go through a mandatory review process,[78] this approach would far better protect consumers from serious harm than today's lightly regulated market. A similar approach, suggested by a former industry scientist, would be to adapt a framework for dietary supplement ingredients similar to the GRAS standard for food additives.[79]

A third phase would address more challenging issues related to claims and inspections. Where all other approaches have failed, the FDA should have special authority in case that products marketed with a specific set of claims are overwhelmingly likely to pose a risk to the public. For example, a very high percentage of products for male sexual enhancement/performance have been found to be spiked with pharmaceuticals or analogues.[80, 81] If other methods cannot protect consumers from unsafe products, the FDA should be able to impose greater restrictions on the use of this claim.

To promote more and better inspections, the FDA requires more resources. In the absence of additional appropriations, a user fee arrangement, similar to what exists for drugs and devices, would provide support for many more inspections than are possible today.

Why would the supplement industry accept any greater authority over dietary supplements by the FDA, let alone new authority with respect to safety? The industry currently faces the risk of small manufacturers tarnishing the image and reputation of the entire market.[82, 83] Media coverage of market failures, such as the 'Supplement Shell Game' series by Alison Young at *USA Today*, are increasing public understanding and pressure for reform.[75] One leading industry attorney recently wrote in *Nutraceuticals World* of the 'perception by those in the mass media, politicians, and regulators that we are a rogue industry that needs to be watched because we cannot be trusted'.[84] Leaders of the industry may recognize that a serious crisis that causes significant harm to consumers could lead to a very different political climate and consideration of measures far more onerous than those outlined here.

Why would healthcare organizations and medical professionals accept anything less than a full FDA premarket review of efficacy claims? Healthcare professionals have come to realize that many have come to rely on dietary supplements and associated perceived health outcomes. It is likely that most clinicians would accept an approach that provides a far greater assurance of safety for their patients.

Conclusion

The nineteenth-century German leader Otto Von Bismarck once said that 'politics is the art of the possible, the attainable - the art of the next best.' Von Bismarck also struggled with obesity. Under the care of his personal physician Dr Ernst Sweninger, Von Bismarck used herbal supplements as part of a holistic treatment regimen and lost more than 40 pounds.[85] He lived to age 83. In the spirit of Von Bismarck, setting aside disputes over the efficacy of dietary supplements might permit serious discussions of safety issues to proceed. The resulting approach might not be perfect, but it could allow for dietary supplement regulation to move past historic obstacles and better protect the public.

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