Author Contributions: Drs Safa and Darrieux had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Both authors. Acquisition of data: Both authors. Analysis and interpretation of data: Both authors. Drafting of the manuscript: Both authors. Critical revision of the manuscript for important intellectual content: Both authors. Administrative, technical, and material support: Both authors. Study supervision: Both authors.

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Balancing the Risks and Benefits of Rituximab

In this issue, Safa and Darrieux1 report a new and serious type of infection after rituximab therapy: cerebral toxoplasmosis. Although rituximab has helped many patients with lymphoma and autoimmune disease for more than 10 years, it has been linked to several major infectious complications.2 Reactivation of hepatitis B, cytomegalovirus disease, and the rare but fatal progressive multifocal leukoencephalopathy are the most infamous of these infections.

Establishing a causal link between rituximab and infectious complications is difficult because most patients receive multiple immunosuppressors, consecutively or even concurrently. Rituximab can be impressively effective in some patients. More than 40% of patients with non-Hodgkin lymphoma3,4 respond and 30% of patients with rheumatoid arthritis5 improve with this drug, whereas only 1% experience serious infections.6 Balancing these rare but alarming adverse effects with the immediate benefits is not easy. As more patients are prescribed this drug, we must remain vigilant to posttrial data on complications and study ways to help patients and physicians make informed decisions that incorporate the rapidly expanding evidence base concerning potential adverse effects.

Eleni Linos, MD, DrPH


RESEARCH LETTER

Health Care Reform

The Frequency and Characteristics of Dietary Supplement Recalls in the United States

Recently, the US Food and Drug Administration (FDA) has identified an emerging trend in which over-the-counter products, represented as dietary supplements, contain hidden ingredients that could be harmful.

See Editor’s Note at end of letter

The FDA defines a dietary supplement as a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet.1 The dietary ingredients in these products may include vitamins, minerals, herbs or other botanical products, amino acids, and substances such as metabolites (eTable; http://www.jamainternalmed.com). In contrast to pharmaceutical products, federal law does not require dietary supplements to undergo stringent review by the FDA before they are marketed.1 However, the FDA does mandate that manufacturers of these products use current good manufacturing practices to ensure quality throughout the manufacturing, packaging, labeling, and storing of these products.1 Despite these safeguards, dietary supplements adulterated with pharmaceutical compounds have continued to enter the marketplace.2 Their use may expose unwitting consumers to potential harm.

Identification of dietary supplements for recall by the FDA may occur through multiple mechanisms, including spot inspection of manufacturers, tips of potentially adulterated products from retailers, and adverse event reports generated by consumers and physicians to name a few.3 Currently, little is known about the extent to which dietary supplements are recalled owing to their potential to cause serious adverse health consequences or death.
Therefore, our objective was to describe the frequency and characteristics of recalls of dietary supplements in the United States.

Methods. Using the FDA Enforcement Reports, we conducted a descriptive study using extracted data for all drug products listed as a dietary supplement with a class I drug recall in the United States from January 1, 2004, to December 19, 2012. Class I recalls are those for which there is a reasonable probability that the use of or exposure to a product will cause serious adverse health consequences or death. Although dietary supplements are not regulated as drugs, they are categorized as such in FDA Enforcement Reports if they are found to contain unapproved regulated substances. For each included drug recall, we extracted the year of the recall, the number of lots recalled, the location of the manufacturer (as mentioned in the recalling firm or manufacturer line of the Enforcement Report), the geographic distribution of recalled products, the presence of associated adverse events, and the type of dietary supplement (weight loss, bodybuilding, sexual enhancement, other). We excluded products that were identical in preparation but differed in their quantity or that were the same product (adulterated with the same agent) but recalled at different times within the same year. We also compared the number of recalled adulterated products contained in the FDA Enforcement Reports with those listed in the FDA Tainted Supplements Report from December 2007 to December 19, 2012.

Results. From January 1, 2004, through December 19, 2012, 465 drugs were subject to a class I recall in the United States. Just over one-half (237 [51%]) were classified as dietary supplements as opposed to pharmaceutical products (Table). Most recalls occurred after 2008 (210 [89%]). Supplements marketed as sexual enhancement products (95 [40%]) were the most commonly recalled dietary supplement product, followed by bodybuilding (73 [31%]) and weight loss products (64 [27%]). Unapproved drug ingredients (237) accounted for all recalls. Fifty-seven recalled products (24%) were manufactured outside of the United States. There were 147 recalls (62%) that involved units distributed internationally. No adverse events related to recalled drugs were noted in the Enforcement Reports.

The FDA Tainted Supplement Report listed 332 adulterated products since December 2007. Only 222 of these products (67%) were recalled by the FDA.

Discussion. Dietary supplements account for just over one-half of class I drug recalls in the United States. Most of these substances are bodybuilding, weight loss, or sexual enhancement products that contain unapproved medicinal ingredients, and almost one-quarter are manufactured outside of the United States.

The passing of the Dietary Supplement Health and Education Act in 1994 permitted dietary supplement manufacturers to bring to market products labeled as supplements without the scrutiny required of pharmaceuticals. This lack of oversight has permitted the introduction of numerous supplement products, often containing unapproved active pharmaceutical ingredients, into the marketplace, which has led to harm, as was exemplified by the use of the supplement Pai You Guo. In these situations, it is incumbent on the FDA to contact the manufacturer of the supplement to trace the source of the product, and initiate a recall. However, a recent investigation by the Office of the Inspector General determined that the FDA does not possess accurate contact information for 20% of supplement manufacturers. This may explain why our study found a large discrepancy between the number of adulterated supplements reported by the FDA and the number that were actually recalled.

The FDA has recently introduced a number of initiatives aimed at mitigating the impact of the most common adulterated supplement products: weight loss, bodybuilding, and sexual enhancement supplements. These initiatives include the creation of multinational enforcement groups, which target the suppliers of these products, as well as widespread media campaigns focusing on improving health professional and consumer awareness of adulterated dietary supplements. Despite these initiatives, products subject to class I recalls, such as Pai You Guo, continue to be readily available for sale, which may be due to an increasingly complex distribution network associated with these products, as well as ineffective communication by the FDA to consumers.
We also found a number of recalled products to be manufactured outside of the United States, where manufacturing practices may not be subject to the same oversight and regulation required of domestic companies. However, most recalled products were manufactured in the United States. Indeed, the FDA has found violations of good manufacturing practices to be rampant in nearly half of the domestic dietary supplement firms it has inspected.

Our study has some limitations. First, our focus on only class I recalls may have led us to underestimate the magnitude of recalls of dietary supplements given their mass availability and the lack of regulation of these products. Second, we were unable to associate the use of many of adulterated supplements with adverse events. However, the FDA is not required to specify whether a recall occurs owing to an adverse event in Enforcement Reports. Finally, it is unclear whether the increase in recalls of dietary supplements is due to improvement in detection by the FDA, improved enforcement by the FDA, or an increase in the number of adulterated supplements that are being marketed.

Recalls of dietary supplements containing unapproved pharmaceutical ingredients are increasing. With over 150 million US residents consuming these products, the challenges posed by this growing and unregulated industry are enormous. To protect the health and safety of the public, increased efforts are needed to regulate this industry through more stringent enforcement and a standard of regulation similar to that for pharmaceuticals. Keeping the status quo may taint the dietary supplement industry as a whole.

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Online-Only Material: The eTable is available at: www.jamainternalmed.com.

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EDITOR’S NOTE

How Can We Know if Supplements Are Safe if We Do Not Know What Is in Them?

Americans spend over $20 billion annually on dietary supplements. Although supplements are regulated by the US Food and Drug Administration (FDA) under the Dietary Supplement Health and Education Act, there is no requirement for supplement manufacturers to demonstrate efficacy or safety of their products prior to marketing them. However, companies may not include unapproved ingredients. It turns out that even this minimal requirement is not fulfilled. Harel et al identified 237 dietary supplements that were recalled by the FDA owing to inclusion of unapproved drug ingredients. Given the limited regulation of these products, it is likely that the number of recalls grossly underestimates the number of products on sale with unapproved ingredients. Dietary supplements should be treated with the same rigor as pharmaceutical drugs and with the same goal: to protect consumer health.

Mitchell H. Katz, MD

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