Presence of Banned Drugs in Dietary Supplements Following FDA Recalls

The US Food and Drug Administration (FDA) initiates class I drug recalls when products have the reasonable possibility of causing serious adverse health consequences or death. Recently, the FDA has used class I drug recalls in an effort to remove dietary supplements adulterated with pharmaceutical ingredients from US markets. Approximately half of all FDA class I drug recalls since 2004 have involved dietary supplements adulterated with banned pharmaceutical ingredients. 1,2

Prior research has found that even after FDA recalls, dietary supplements remain available on store shelves. 3,4 However, it is not known if the supplements on sale after FDA recalls are free of the adulterants. In the present study, dietary supplements purchased at least 6 months after FDA recalls were analyzed to determine if banned drugs were still present.

Methods | Dietary supplements were analyzed if they met the following inclusion criteria: (1) recalled due to adulteration with pharmaceutical ingredients between January 1, 2009, and December 31, 2012; (2) available for purchase in July or August 2013 directly from websites of supplement manufacturers or retailers (as opposed to general e-commerce sites such as Amazon.com, eBay Inc, or Alibaba Group); and (3) the supplement name, manufacturer, and distributor listed on the purchased supplement was identical to the information provided in the FDA recall.

Dietary supplements were analyzed by Flora Research Laboratories (J.N.-K.). Samples were labeled with the marketing claim on the supplement label (eg, weight loss, sexual enhancement, or sports enhancement), but did not include the supplement name, manufacturer, and prior FDA findings.

Analyses were performed using the same methods that the FDA’s field laboratories use to screen for clandestine adulteration. In short, dietary supplements were analyzed using either gas chromatography mass spectrometry or liquid chromatography tandem mass spectrometry in data-triggered mode. Adulterants, except for anabolic steroids, were confirmed against a standard using retention time, mass spectrum, and UV spectrum.

Results | The FDA recalled 274 dietary supplements between January 1, 2009, and December 31, 2012. Twenty-seven of the 274 recalled supplements (9.9%) met our inclusion criteria and were analyzed. Supplements were purchased a mean (SD) of 34.3 (11.5) months after the FDA recall (range, 8-52 months). Seventy-four percent of supplements (20/27) were produced by US manufacturers.

One or more pharmaceutical adulterant was identified in 66.7% of recalled supplements still available for purchase (18/27; Table). Supplements remained adulterated in 85% (11/13) of those for sports enhancement, 67% (6/9) for weight loss, and 20% (1/5) for sexual enhancement. Of the subset of supplements produced by US manufacturers, 65% (13/20) remained adulterated with banned ingredients.

Sixty-three percent of analyzed supplements (17/27) contained the same adulterant identified by the FDA. Six of the 27 (22.2%) supplements contained 1 or more additional banned ingredients not identified by the FDA (Table). Some supplements contained both the previously identified adulterant as well as additional pharmaceutical ingredients. Banned substances identified in recalled supplements included sibutramine, sibutramine analogs, sildenafil, fluoxetine, phenolphthalein, aromatase inhibitor, and various anabolic steroids. One novel adulterant, benzyl sibutramine, was first described as recently as 2013. 6

Discussion | To our knowledge, this is the first study to determine if adulterants remain in supplements sold after FDA recalls. We found that 66.7% of recalled supplements still available for purchase at least 6 months after FDA recalls remained adulterated with banned ingredients.

Our study has several limitations. First, we limited testing to common adulterants expected based on marketing claims (eg, weight loss supplements were tested for adulterants commonly found in weight loss products). Second, our analyses may have failed to detect recently introduced drug analogs. Third, although every effort was made to purchase recently manufactured supplements, it is not known if all supplements were manufactured after the FDA recall.

Action by the FDA has not been completely effective in eliminating all potentially dangerous adulterated supplements from the US marketplace. More aggressive enforcement of the law, changes to the law to increase the FDA’s enforcement powers, or both will be required if sales of these products are to be prevented in the future.

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Author Contributions: Dr Cohen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cohen. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Cohen.
Table. Pharmaceutical Adulterants Identified in Recalled Dietary Supplements Purchased at Least 8 Months After US Food and Drug Administration (FDA) Recalls

<table>
<thead>
<tr>
<th>Recalled Supplement</th>
<th>Date of FDA Recall</th>
<th>Date Purchased</th>
<th>Expiration Date on Purchased Supplement</th>
<th>Adulterant Found by FDA</th>
<th>Adulterant Found After FDA Recall</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a, 17α Methastrol</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>January 2014</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Anabolic steroid</td>
</tr>
<tr>
<td>4-ad</td>
<td>September 16, 2010</td>
<td>July 2013</td>
<td>March 2015</td>
<td>Aromatase inhibitor</td>
<td>None identified</td>
</tr>
<tr>
<td>Açai-Man Mangosteen</td>
<td>February 3, 2012</td>
<td>July 2013</td>
<td>Not available</td>
<td>Tadalafil</td>
<td>None identified</td>
</tr>
<tr>
<td>Botanical Slimming 100% Natural Softgel</td>
<td>September 2, 2011</td>
<td>August 2013</td>
<td>Not available</td>
<td>Sibutramine</td>
<td>Sibutramine</td>
</tr>
<tr>
<td>E-pol: Insulinsified</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>Not available</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Two anabolic steroids</td>
</tr>
<tr>
<td>EverSlim</td>
<td>February 1, 2012</td>
<td>July 2013</td>
<td>January 2018</td>
<td>Sibutramine</td>
<td>None identified</td>
</tr>
<tr>
<td>FINAflex SS0-XD</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>June 2014</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Two anabolic steroids</td>
</tr>
<tr>
<td>Forged Extreme Mass</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>November 2011</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Anabolic steroid</td>
</tr>
<tr>
<td>Joyful Slim</td>
<td>July 22, 2010</td>
<td>July 2013</td>
<td>December 2013</td>
<td>Desmethylsibutramine (an analog of sibutramine)</td>
<td>None identified</td>
</tr>
<tr>
<td>M-Drol</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>Not available</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Anabolic steroid</td>
</tr>
<tr>
<td>Magic Power Coffee</td>
<td>June 25, 2010</td>
<td>August 2013</td>
<td>February 2015</td>
<td>Hydroxythiohomosildenafil (an analog of sildenafil)</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Massdrol</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>Not available</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Anabolic steroid</td>
</tr>
<tr>
<td>Mince Belle</td>
<td>February 3, 2012</td>
<td>July 2013</td>
<td>Not available</td>
<td>Sibutramine</td>
<td>None identified</td>
</tr>
<tr>
<td>Novedex XT</td>
<td>January 15 and October 7, 2010</td>
<td>July 2013</td>
<td>July 2013</td>
<td>Aromatase inhibitor and steroid or steroid-like compound or analog</td>
<td>Aromatase inhibitor and an anabolic steroid</td>
</tr>
<tr>
<td>On Cycle II Hardcore</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>Not available</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Two anabolic steroids</td>
</tr>
<tr>
<td>P-Plex</td>
<td>November 3, 2009, and January 15, 2010</td>
<td>August 2013</td>
<td>October 2012</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Anabolic steroid impurities</td>
</tr>
<tr>
<td>Pandora: Sexual Enhancer for Women</td>
<td>December 23, 2010</td>
<td>July 2013</td>
<td>October 2013</td>
<td>Analog of sildenafil</td>
<td>None identified</td>
</tr>
<tr>
<td>RockHard Weekend</td>
<td>November 9, 2009, and December 22, 2010</td>
<td>July 2013</td>
<td>March 2014</td>
<td>Sulfoaidenafil (an analog of sildenafil)</td>
<td>None identified</td>
</tr>
<tr>
<td>Testra-flex</td>
<td>January 15, 2010</td>
<td>July 2013</td>
<td>May 2014</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Anabolic steroid</td>
</tr>
<tr>
<td>Slim-30</td>
<td>July 16 and August 18, 2010</td>
<td>July 2013</td>
<td>December 2015</td>
<td>Desmethyl sibutramine (an analog of sibutramine)</td>
<td>None identified</td>
</tr>
<tr>
<td>Slim Forte Slimming Capsule</td>
<td>July 27, 2011</td>
<td>July 2013</td>
<td>April 2018</td>
<td>Sibutramine</td>
<td>Sibutramine, phenolphthalein</td>
</tr>
<tr>
<td>Slim Xtreme Herbal Slimming Capsule</td>
<td>May 11, 2011</td>
<td>July 2013</td>
<td>January 2015</td>
<td>Sibutramine</td>
<td>Sibutramine, phenolphthalein, benzyl sibutramine (an analog of sibutramine)</td>
</tr>
<tr>
<td>Stamina-RX</td>
<td>June 15, 2009</td>
<td>August 2013</td>
<td>September 2014</td>
<td>Benzamidenedafil (an analog of sildenafil)</td>
<td>None identified</td>
</tr>
<tr>
<td>Trenadrol</td>
<td>November 3, 2009</td>
<td>August 2013</td>
<td>Not available</td>
<td>Steroid or steroid-like compound or analog</td>
<td>Anabolic steroid</td>
</tr>
<tr>
<td>X-TREN</td>
<td>November 3, 2009, and January 15, 2010</td>
<td>August 2013</td>
<td>September 2014</td>
<td>Steroid or steroid-like compound or analog</td>
<td>None identified</td>
</tr>
</tbody>
</table>

* Information available at http://www.fda.gov/ForConsumers/ProtectYourself/HealthFraud/ucm255499.htm.

b May have been recalled more than once.

c May have included more than 1 adulterant.

Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Maller, DeSouza. Obtained funding: Cohen. Administrative, technical, or material support: Maller, Neal-Kababick. Study supervision: Cohen.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr Maller reported receiving personal fees from NY State Senator Jeffrey Klein and SSP Nutrition outside of the submitted work. Mr Neal-Kababick reported being the vice chair of the US Pharmacopeia expert panel on Adulteration of Dietary...
Supplements with Drugs and Drug Analogues; reported being a co-owner of Flora Research Laboratories (some of the clients are dietary supplement manufacturers); and reported serving as an expert witness in cases involving the investigation of quality issues in the production of dietary supplements. No other disclosures were reported.

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Correction: This article was corrected on November 4, 2014, to fix the name of the study funder.


COMMENT & RESPONSE

Insulin vs Sulfonylureas for Second-Line Diabetes Treatment

To the Editor Dr Roumie and colleagues1 reported that compared with sulfonylureas the addition of insulin to metformin to improve glycemic control was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality in patients with diabetes mellitus. Although the results presented require verification in carefully designed clinical trials, we have some concerns about the current analyses.

Roumie et al1 stated that subgroup analyses stratifying by age were consistent with the primary analysis. However, eFigure 3 showed that the hazard ratio (HR) for cardiovascular events or death was 1.14 (95% CI, 0.82-1.59) for patients younger than 65 years, whereas for those aged 65 years or older, the HR was 1.51 (95% CI, 1.19-1.92). For the composite death outcome, the HR was 1.28 (95% CI, 0.85-1.97) for patients younger than 65 years, whereas for those aged 65 years or older, the HR was 1.66 (95% CI, 1.29-2.14). Contrary to the conclusion made by the authors, the results suggest that insulin added to metformin is safe among patients younger than 65 years but appears to be hazardous in older patients with diabetes.

Part of the explanation may be differences in types of insulin used and hypoglycemia by age group. Of the patients in the metformin plus insulin group, 47% used long-acting agents only; 22%, both long- and short-acting agents; 17%, premixed insulin; and 11%, short-acting agents only. Although premixed insulin use in older adults can increase the risk of hypoglycemia compared with long-acting analogs,2 even the choice of regular or analog insulin can influence the frequency of hypoglycemic episodes when multiple injections are used.3 Thus, the type of insulin chosen for older patients with diabetes should be taken into consideration in such database analyses.

In addition, below a hemoglobin A1c level of 8%, the risk of treatment-induced hypoglycemia increases.4 Because mean hemoglobin A1c levels were 7% among sulfonylurea users and 6.9% among insulin users in this study, missing hypoglycemia data are of concern. Even though Roumie et al1 used an extensive database, they were unable to obtain data on hypoglycemia frequency, especially the number of severe events requiring hospital admission.

Such information is essential for appropriate interpretation of the study. Although sulfonylurea drugs can also increase the risk hypoglycemia of among older patients, comparative data are still required.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


In Reply We agree with Drs Tasci and Safer that the risk of metformin and insulin compared with metformin plus sulfonylurea as a second-line diabetes treatment after failure of metformin monotherapy may differ in certain populations. They point to eFigure 3 that shows a statistically significant increased risk in persons aged 65 years or older and no statistically significant increase in younger persons.

However, the confidence intervals for the HRs in the 2 age groups have considerable overlap and a formal test for interaction between metformin plus insulin and age is not significant (P = .22). Thus, we have not proven significant differences in risk by age. The numerical differences observed could represent real differences or simply chance variation in the estimated associations.