



**Public health concerns for anti-obesity medicines imported for personal use through the Internet: a cross-sectional survey**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-000854
Article Type:	Research
Date Submitted by the Author:	11-Jan-2012
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<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Global health, Pharmacology and therapeutics, Nutrition and metabolism
Keywords:	PUBLIC HEALTH, NUTRITION & DIETETICS, MEDICAL LAW, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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1     **Public health concerns for anti-obesity medicines imported for**  
2           **personal use through the Internet: a cross-sectional survey**

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11    **Running title:** Quality of online anti-obesity medicines

12    **Word counts:** 3,088

13    **Key Words:** Quality, counterfeit medicine, public health, the Internet, anti-obesity

14    medicine

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16 **ABSTRACT**

17 **Objectives:** To explore the circulation of anti-obesity medicines via the Internet and their  
18 quality.

19 **Design:** Cross-sectional survey.

20 **Setting:** Internet pharmacies and pharmaceutical suppliers accessible from Japan.

21 **Participants:** Anti-obesity medicines were purchased using relevant keywords on Japanese  
22 Google search engine. Blogs and advertisement-only sites were excluded.

23 **Primary and secondary outcome measures:** The authenticity of the samples was investigated  
24 in collaboration with the manufacturers of the samples and medicine regulatory authorities. of  
25 Quality of the samples were performed by pharmacopoeial analyses utilizing high performance  
26 liquid chromatography.

27 **Results:** Eighty-two samples were purchased from 36 internet sites. Approximately half of the  
28 sites did not mention a physical address, and 45% of the samples did not contain a package  
29 insert. A variety of custom declarations were made for the shipments of the samples: personal  
30 health items, supplement, medicines, general merchandise, tea and others. Three of the samples  
31 were identified as counterfeits and did not contain any active ingredients according to the  
32 chemical analyses. Two of these samples were confirmed as counterfeits by the manufacturer of  
33 the authentic products. The manufacturer of the other sample did not respond to our request for

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6 34 an authenticity check even after several communication attempts. These counterfeit cases have  
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9 35 been reported at the rapid alert system of Western Pacific Region of the World Health  
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12 36 Organization.

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15 37 **Conclusion:** Many counterfeit and unapproved anti-obesity medicines may be easily bypassing  
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18 38 regulatory checks during shipping and are widely circulated through the Internet. Regulatory  
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21 39 authorities should take measures to prevent these medicines from entering countries to  
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24 40 safeguard their citizens.

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6 49 **ARTICLE SUMMARY**  
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9 50 **Article Focus**

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12 51 • Quality of online anti-obesity medicines.  
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15 52 • Circulation of unapproved anti-obesity medicines via the Internet.  
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18 53 **Key Messages**

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21 54 • Counterfeit and substandard anti-obesity medicines, orlistat are identified.  
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24 55 • False and vague custom declarations were made by some of the shipping  
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26 56 companies to by-pass regulatory checks of unapproved online medicines.  
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29 57 **Strength and Limitations**

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32 58 Small sample size and low authenticity response rate are limitations of this study.  
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35 59 However, the study provides valuable information for regulatory authorities on how  
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38 60 unapproved and counterfeit medicines are being circulated through the Internet.  
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41 61 Concerted efforts of authentic manufacturers and medicine regulatory authorities are  
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44 62 must to combat counterfeits and ensure access of quality medicines to online consumers.  
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6 **63 INTRODUCTION**  
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9 64 Over the past decade, the Internet has become an integral part of life for a variety of uses.

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11 65 Approximately 60% of Internet users in some developed countries utilize the Internet for their

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14 66 health related activities.[1, 2] In fact, when Internet users were asked about specific searches

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17 67 related to health, such as diet and fitness information or health insurance materials, 80% of the

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20 68 users in a 2002 survey said that they had performed these types of searches.[1] According to a

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23 69 survey taken in Japan, a majority (86.3%) of the medicines imported for personal use were

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26 70 purchased through the Internet.[3] However, according to World Health Organization, more than

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29 71 50% of the medicines from Internet sites, which often conceal their physical address, may be

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32 72 counterfeit or of substandard quality.[4]  
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74 Obesity is becoming a major public health epidemic in this century and is associated with an

75 increased risk for a number of health problems, such as hypertension, dyslipidemia, type 2

76 diabetes, and cardiovascular diseases.[5] The prevalence of obesity and its associated conditions

77 are increasingly affecting both developed and developing countries over the last few decades.[6]

78 Studies suggest that primarily adolescent and adult males are overweight or obese in Japan.[7]

79 Recommended strategies for managing weight and obesity include lifestyle changes with

80 appropriate dietary management and exercise. However, individuals with an isolated BMI $\geq$ 30

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6 81 kg m<sup>-2</sup> or a BMI>27 kg m<sup>-2</sup> with co-morbidities such as type 2 diabetes, cardiovascular  
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9 82 diseases, and obstructive sleep apnea, should receive pharmacotherapy as well.[8] Among the  
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12 83 available anti-obesity medicines, phentermine, diethylpropion and orlistat are approved by the  
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15 84 U.S. Food and Drug Administration, but sibutramine has been withdrawn from the market.[9,  
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18 85 10] Of these anti-obesity medicines, only mazindol has been approved for use in Japan.[11]  
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21 86 However, several of these anti-obesity medicines are among those that are frequently imported  
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24 87 into Japan for personal use.[12]  
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29 89 The online purchase of medicine through the Internet is a growing and convenient practice for  
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32 90 many consumers. This practice has also become one of the most popular, easiest and safest  
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35 91 routes for counterfeit medicine traders.[4, 13-15] Because lifestyle medicines are frequently  
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38 92 targeted by counterfeiters, a collaborative investigation between the Ministry of Health and  
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41 93 Labour Welfare (MHLW), Japan; Kanazawa University, Kanazawa; and Doshisha Women's  
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44 94 College, Kyoto, Japan was conducted to survey the quality of anti-obesity medicines that were  
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47 95 purchased through online medicine sites. This investigation also provided an understanding of  
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50 96 the process by which unapproved medicines are being imported for and used by consumers in  
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6 99 **METHODS**

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9 100 **Study design**

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11 101 Quality of online anti-obesity medicines was assessed using an online cross-sectional survey  
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13 102 during August 2009.  
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21 104 **Selection of Internet sites and sample collection**

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23 105 The Japanese keywords personal import agent, diet, and anti-obesity medicines were used on  
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25 106 the Japanese Google search engine (www.google.co.jp) to find online pharmacies or suppliers  
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27 107 that offer anti-obesity medicines. Searches were also made on websites that advertise and sell  
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29 108 counterfeit Cialis, Levitra and Viagra. The physical characteristics of original and counterfeit  
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31 109 Cialis and Levitra were both identified earlier by the Ministry of Health, Japan, and information  
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33 110 on websites that sell counterfeit Viagra was provided by Pfizer.[16] After the exclusion of blogs  
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35 111 and advertisement-only sites, 36 sites were chosen for the purchase of anti-obesity medicines.  
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37 112 Some of the criteria used in choosing the sites included the absence of a physical address and  
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39 113 the presence of suspicious advertisements. A list of overweight/anti-obesity medicines was  
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41 114 sought on each of the selected sites. Priority rankings were made of the list of medicines  
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43 115 according to their vertical or horizontal placement on the web pages. Samples of the anti-obesity  
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45 116 medicines were purchased from selected sites according to the smallest priority number found  
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6 117 for a medicine that had not been purchased from a previous website.  
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11 119 Information on the site's name, URL, compliance with Japanese rules of "Act on Specified  
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14 120 Commercial Transaction" (ASCT), e-mail address, the name of the product and other  
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17 121 information such as the dosage, efficacy and side effects, recommendation on consultation with  
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20 122 doctors or pharmacists or opportunities for consultation were recorded while examining the sites  
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23 123 from which at least one product was purchased.  
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29 125 **Observational analysis**  
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32 126 All of the samples were given distinct codes when the shipments were received. The name of  
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35 127 the product, dosage form, content information from the printed label, the manufacturers' name  
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38 128 and address, the country of origin, the manufacture and expiration dates, lot, registration and  
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41 129 license numbers, Japanese manual, information from the shipping company, the sending country,  
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44 130 the date of shipment and arrival, and customs declaration notations were recorded for each of  
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47 131 the samples.  
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52 133 **Chemical analysis**  
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55 134 Pharmacopoeial procedures for the analysis of the samples were established and performed  
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6 135 using high performance liquid chromatography (HPLC), which are described briefly below.  
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11 137 Preparation of the sample solutions

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14 138 Randomly selected capsules of orlistat and sibutramine samples were weighed accurately. After

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17 139 each capsule was weighed, the contents were removed, and the empty capsule shells were

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20 140 subsequently weighed. The difference between the weight of the whole capsule and the capsule

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23 141 shell was assumed to be the weight of the contents. Approximately 80 ml of methanol was

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26 142 added to the capsule's contents, and the mixture was sonicated for 30 min. After sonication,

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29 143 methanol was then added to a volume of 100 ml. The resulting solutions were filtered through a

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32 144 membrane filter (pore size: 0.45  $\mu\text{m}$ ) and used as the sample solutions.  
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38 146 To prepare sample solutions of lovastatin, benfluorex and rimonabant tablets, randomly chosen

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41 147 tablets were weighed accurately and subsequently crushed separately into powder.

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44 148 Approximately 80 ml of methanol was added to the powder, and the solutions were sonicated

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47 149 for 30 min. Methanol was added to each of the solutions to a volume of 100 ml. The resulting

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50 150 solutions were filtered through membrane filters (pore size: 0.45  $\mu\text{m}$ ) and used as the sample

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53 151 solutions.  
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6 153 Preparation of standard solutions  
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9 154 Three consecutive strengths of standard solutions were prepared by dissolving 0.375 mg, 0.75  
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12 155 mg and 1.50 mg of orlistat; 0.050 mg, 0.100 mg and 0.200 mg of sibutramine; 0.100 mg, 0.200  
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15 156 mg and 0.500 mg of lovastatin; 0.100 mg, 1.50 mg and 2.00 mg of benfluorex; 0.100 mg, 0.200  
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18 157 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.  
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23 159 Assay condition  
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26 160 Ten microliters of each sample solution and standard solution was placed in vials and assayed  
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29 161 using a photodiode array of 225 nm wavelength (200-400 nm range for spectra) with a stainless  
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32 162 steel column with a 4.6 mm internal diameter and 15 cm length packed with octadecylsilanized  
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35 163 silica gel for liquid chromatography (5  $\mu$ m particle diameter) used with Mightysil RP-18 GP  
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38 164 150-4.6. The column temperature was maintained at 45°C. A mixture of methanol and phosphate  
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41 165 buffer, pH 7.0 (17:3) was used as the mobile phase at a flow rate of 1.2 ml/min.  
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47 167 **Authenticity investigation**  
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50 168 A catalogue and a questionnaire for all the samples were created that included the information  
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53 169 from the printed labels of the product packages. The printed information was also checked  
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56 170 against the information on the manufacturers' websites. The questionnaires were sent to the  
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6 171 appropriate manufacturers with a portion of the samples for verification of their authenticity.  
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9 172 The regulatory authorities for medicine in the country of origin were also contacted to verify the  
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12 173 legitimacy of the products and their approval for marketing. After considering the WHO  
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15 174 definition of counterfeit medicines, the gathered information was analyzed to determine the  
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18 175 authenticity of the individual samples and their manufacturers.[17, 18]  
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24 177 **Statistical analysis**  
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27 178 Because of the small size of the sample, descriptive statistical analysis was performed using  
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30 179 Microsoft Excel.  
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36 181 **RESULTS**  
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39 182 A total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet  
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42 183 sites. Some of these products were shipped in divided shipments and treated as distinct samples.  
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45 184 Of the selected internet sites, 15 sites did not show a physical address, and six, two and nine of  
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48 185 the web sites advertised counterfeit Cialis, Levitra and Viagra, respectively. Two of the sites  
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51 186 with fake Cialis and Viagra also did not show a physical address. Four of the websites were  
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54 187 hosted by domestic shipping companies.  
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6 189 **Information available on the web sites**  
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9 190 Different levels of compliance with ASCT were observed throughout all (36) of the web sites.  
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11 191 For instance, all (100%) of them mentioned the selling price, shipping charges for the goods,  
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13 192 and methods of payment. However, only 21 (58.3%) of them provided telephone numbers, and  
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15 193 only 17 (47.2%) of them mentioned a physical address.  
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23 195 Information for e-mail addresses and shipment procedures were presented on all of the selected  
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25 196 sites. However, only 21 (58.3%) of them encouraged consumers to consult with a physician or  
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27 197 pharmacist. Consultation services were available at two (5.5%) of the sites. Dosage and  
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29 198 administration, effects and efficacy, and side effects related to the products were explained in 18  
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31 199 (50%), 23 (63.8%) and 17 (47.2%) of the sites, respectively, despite the prohibition on  
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33 200 advertisements for unapproved medicines.  
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42 202 **Information provided with the samples**  
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46 203 Upon examination of the printed materials, the languages of the package inserts were found to  
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48 204 be in English for 17.1% of the samples, Chinese for 15.9%, both Chinese and Korean for 12.2%,  
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50 205 both English and Chinese for 4.9%, Turkish for 2.4%, both English and Thai for 1.2%, and  
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52 206 English, Chinese and Russian for 1.2% of the samples. However, 45.1% (37) of the samples did  
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6 207 not have any package inserts.  
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11 209 **Shipment of the samples**

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14 210 Samples were sent by 29 different shipping companies. The majority (13 companies) shipped  
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17 211 from China, and the second largest group was from India (4 companies). Others were shipped  
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20 212 from the USA (3), Japan (2), Thailand (2), Switzerland (1), Hong Kong (1), Cambodia (1), the  
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23 213 Fiji Islands (1), and Puerto Rico (1). The customs declaration was 'health product/personal  
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26 214 health items' for 20 (24.4%) of the samples, 'supplement' for 13 (15.9%) of the samples,  
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29 215 'medicine' for 10 (12.2%) of the samples and the actual name of the product in 2 (2.4%) cases.  
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32 216 However, 12 (14.7%) of the samples were shipped with a declaration of general merchandise  
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35 217 and/or tea, 11 (13.4%) of them declared 'other' and 14 (17.1%) of them did not mention  
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38 218 anything as the declaration. Interestingly, one representative from an importing agent of a diet  
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41 219 medicine clinic (Sabairato Yanhee MD and clinic, <http://www.gop23.com>) inquired over the  
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44 220 telephone regarding the purpose for our purchase of the medicine and asked if we had any  
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47 221 relationship with the MHLW, Japan; they did not sell their products to us.

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52 223 **Sample characteristics**

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55 224 Of the 82 samples, 43 (52.4%) were advertised on the websites as containing sibutramine  
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6 225 hydrochloride and 15 (18.3%) were advertised as orlistat. Rimonabant, benfluorex, and  
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9 226 lovastatin were advertised to be in two (2.4%) of the samples. Rhei rhubarb was said to be in  
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12 227 one, and the remaining 17 (20.7%) samples were advertised to be herbal products. The results of  
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15 228 the rhubarb and herbal products will be reported elsewhere. Out of the 64 synthetic products, 58  
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18 229 samples from 19 different products were prescription medicines, five brands of orlistat were  
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21 230 over-the-counter medicines, and one sample, Daidai hua, was marketed as a natural supplement.  
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24 231 However, this product was advertised as sibutramine by its agent, and the sample actually  
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27 232 contained sibutramine as shown by chemical analysis.

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### 31 32 234 **Quality analysis**

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35 235 Quantitative analysis by HPLC showed that all (21) of the samples of sibutramine were in the  
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38 236 acceptable range (90%-110%) except one (mean content percentage of  $60.2 \pm 7.6$ ). No active  
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41 237 ingredient was detected in three out of the 13 samples of orlistat that we tested (Figure 1). These  
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44 238 three samples were identified to be counterfeit. Of these three counterfeit samples, two were  
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47 239 found to be Xenical after analysis by the researchers and the manufacturer of the genuine  
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50 240 products. No active ingredient was detected in the last sample, only starch (Figure 1). The other  
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53 241 counterfeit sample contained unknown excipients. None of the samples of lovastatin, benfluorex  
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56 242 or rimonabant failed the HPLC analysis.

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244 **Authenticity investigation**

245 Responses to our requests for authentication were received from only five of the 20  
 246 manufacturing companies of the genuine samples. According to the responses that we received,  
 247 all of the responding manufacturers were GMP compliant. Of the 12 reported samples, two of  
 248 the orlistat samples (Xenical) from the same manufacturer were confirmed to be counterfeit  
 249 (Table 1).

250 Table 1. Results of Authenticity Investigation

Active ingredient	Country of Authorized Marketer	Genuine	Counterfeit	Manufacturing
		sample	sample	License
Orlistat (60 mg)	USA	5	0	YES
Benfluorex (150 mg)	France	2	0	YES
Rimonabant (20 mg)	India	1	0	YES
Orlistat (120 mg)	Switzerland	1	2	YES
Rhei Rhubarb	China	1	0	YES
*Orlistat (120 mg)	India	0	1	Unknown

251 \* labeled manufacturer did not reply



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9 253 The counterfeit samples were purchased at [www.kenkoclinic.com](http://www.kenkoclinic.com) and sent to us from Puerto  
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12 254 Rico. They bore the same manufacture and expiration dates (MFD: 02/2011 and EXP: 02/2011,  
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15 255 Figure 2) on their blisters, which had not yet occurred at the time of our investigation. The  
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18 256 printed information on the blisters of the counterfeits was a different color with a similar but  
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21 257 slightly different logo (Figure 3).  
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26 259 Telephone communications were made to the manufacturer of Zenigal (orlistat 120 mg) in India,  
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29 260 which did not contain any of the active ingredients that had been claimed on the product labels.  
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32 261 However, the manufacturer did not respond after several communication attempts. This  
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35 262 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of  
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38 263 counterfeit medicines at the rapid alert system of the Western Pacific Region of the World  
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41 264 Health Organization.  
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46 266 Responses were received from the medical regulatory authorities of three countries (Germany,  
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49 267 Switzerland and USA) for five of the manufacturers. Their responses stated that only orlistat has  
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52 268 approval to be manufactured in Switzerland. Approval for the manufacture of sibutramine in  
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55 269 Germany was suspended in January 2010, and it was not approved for use in the USA.  
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6 270 **DISCUSSION**

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9 271 **Provided information on the samples**

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11 272 According to the Pharmaceutical Affairs Law in Japan, advertising of unapproved medicines is  
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13 273 prohibited, and Customs should seize any shipment of prescription medicines when the amount  
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15 274 exceeds more than a one-month dose or any non-prescription medicines that exceed more than a  
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17 275 two-month dose. However, at least some of the samples in this study that exceeded the approved  
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19 276 amount for shipment made it through the regulatory checks during shipping.[19] Surprisingly, at  
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21 277 least four of the shipping companies are conducting business in Japan. Contact information was  
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23 278 not provided on many of the sites (52.8%), which seemingly contradicts ASCT.[20] According  
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25 279 to our study, nearly fifty percent of the sites mentioned dosage administration, effects or  
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27 280 side-effects of the medicines, which are not permitted by the pharmaceutical affairs laws (PAL)  
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29 281 in Japan.[19] As found in many previous studies on e-medicines, approximately 50% of the  
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31 282 samples did not contain a package insert.[21-25] Moreover, several of the weight-loss products  
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33 283 may contain harmful or contraindicated ingredients.[16, 21]

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49 285 **Approval status of the products**

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51 286 The majority of the study samples were sibutramine, which is a selective inhibitor of the central  
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53 287 neuronal reuptake of serotonin and noradrenaline and reduces food intake and body weight.[26]  
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6 288 However, after conclusion of the safety review of sibutramine, the European Medicines Agency  
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9 289 (EMA) has suspended its marketing authorization in the European Union (EU).[27] A recently  
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12 290 published study reported that generic Figurer (sibutramine 10 mg), even though it has not been  
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15 291 reviewed by the responsible government (USA, the exporting nation), is freely circulating via  
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18 292 the Internet, which is a serious concern for public health.[22] According to the medicine  
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21 293 regulations of Hong Kong, Figurer does not need manufacturing authorization because the  
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24 294 medicine is manufactured in a foreign country. The authorization status of Ali (orlistat 60 mg) as  
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27 295 a prescription medicine has been recommended to transition to a non-prescription medicine in  
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30 296 the EU.[28] In a questionnaire conducted by community pharmacists in Great Britain, orlistat is  
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33 297 suspected to be misused by consumers, as stated in their responses.[29] Similarly, safety profiles  
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36 298 of other anti-obesity agents are generating controversy in different parts of the world.[30-33]  
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39 299 Even though all the anti-obesity agents sampled in this survey are unapproved in Japan, it is  
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42 300 possible that anyone can procure these items without declaring the actual contents during  
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45 301 shipping.

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### 48 49 303 **Authenticity and quality of the samples**

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52 304 As similarly shown in previous studies, we observed low rates of authenticity.[34] Responses  
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55 305 from only five (25%) of the manufacturers for 14.6% of the samples were received. The  
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6 306 counterfeit samples identified in this survey were confirmed by the manufacturer of the  
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9 307 corresponding genuine products. Counterfeiting of anti-obesity medicines, particularly orlistat,  
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12 308 has been previously reported.[35, 36] Based on the external characteristics of the counterfeits,  
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15 309 these products most often differ in their printed information, design, color, etc. from those of the  
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18 310 genuine drugs.[37, 38] As shown in some other studies, the counterfeits detected in this survey  
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21 311 did not contain any active ingredients.[34, 39] It is not clear why the manufacture of Zenigal,  
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24 312 which failed the content analysis, did not respond to our authentication request. In such a case, it  
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27 313 can be assumed that the manufacturer is already aware of the distribution of low-quality  
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30 314 products in the pharmaceutical market. Several reports suggest that patients have sought  
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33 315 medical treatment for life-threatening complications after the consumption of fake or  
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36 316 substandard medicines purchased online.[40] When products are purchased through the Internet  
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39 317 and the sites are not sufficiently regulated, customers are left to accept the consequences.

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44 319 One of the limitations of the study might be small sample size, which may restrict study  
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47 320 findings to Japan. Further evaluation with a representative sample may provide more  
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50 321 information on the extent of the problem. Low response rate of authenticity investigation may  
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53 322 also be considered as a limiting factor. However, better communication and cooperation among  
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56 323 authentic manufacturers and medicine regulatory authorities may increase response rate and

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6 324 generate more information to counteract against counterfeits.  
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## 11 326 **CONCLUSIONS**

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14 327 It is evident from this study that counterfeit, unapproved and suspended anti-obesity medicines  
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17 328 are circulating via the Internet. Because of gaps and the insufficient monitoring system of  
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20 329 imports for personal use in the rapidly growing e-commerce environment, these medicines can  
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23 330 easily enter into the distribution channels for pharmaceuticals and may pose health hazards for  
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26 331 consumers.  
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32 333 **Acknowledgements** We gratefully acknowledge the cooperation received from the staff of  
33  
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35 334 MHLW. Additionally, we thank Ms. Hitomi Tabata for her cooperation in this work.  
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41 336 **Funding** This study was supported by Health and Labour Sciences Research Grants from the  
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44 337 MHLW, Japan.  
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50 339 **Competing interests** The authors declare no conflict of interest.  
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6 342 **Authors' contribution** MHK, TT, YN, and KK participated in the conception and design of the  
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9 343 study; TT, YN and KK participated in sampling activities and analysis of the samples; MHK, TT,  
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11 344 YN, NY, HT and KK participated in data analysis and interpretation of results. MHK wrote the  
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14 345 first draft of the manuscript. All authors contributed in the critical review of the draft manuscript,  
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17 346 editing and finally approved its submitted version.  
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23 348 **Data sharing statement** No additional data available.  
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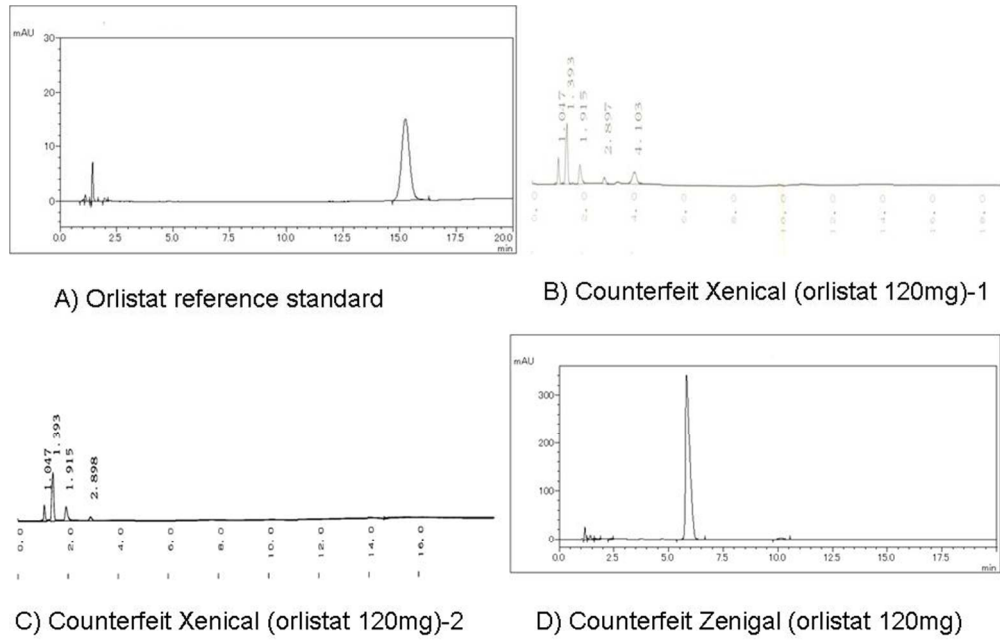


Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples  
254x190mm (96 x 96 DPI)

ew only

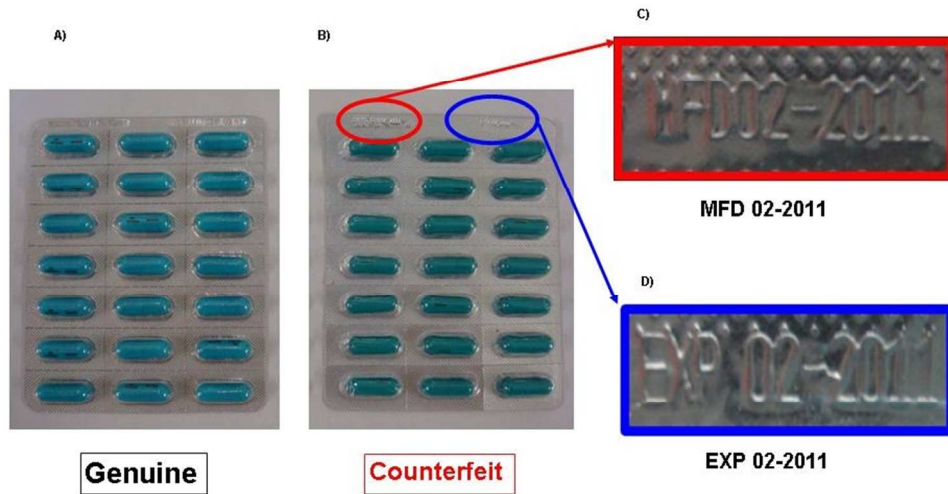


Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)  
254x190mm (96 x 96 DPI)

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Figure 3. Reverse side of blister: A) Logo of genuine sample, B) Logo of counterfeit sample  
254x190mm (96 x 96 DPI)

Review only



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	N.A.
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	N.A.
		(c) Explain how missing data were addressed	N.A.
		(d) If applicable, describe analytical methods taking account of sampling strategy	N.A.
		(e) Describe any sensitivity analyses	N.A.
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13
		(b) Give reasons for non-participation at each stage	11-13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14
		(b) Indicate number of participants with missing data for each variable of interest	13-14
Outcome data	15*	Report numbers of outcome events or summary measures	14-16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N.A.
		(b) Report category boundaries when continuous variables were categorized	N.A.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	17-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



**Public health concerns for anti-obesity medicines imported for personal use through the Internet: a cross-sectional study**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-000854.R1
Article Type:	Research
Date Submitted by the Author:	09-Mar-2012
Complete List of Authors:	Khan, Mohiuddin; Kanazawa University, Drug Management and Policy Tanimoto, Tsuyoshi; Doshisha Women's College, Nakanishi, Yoko; Public Health Center, ; Kanazawa University, Drug Management and Policy Yoshida, Naoko; Kanazawa University, Drug Management and Policy Tsuboi, Hirohito; Kanazawa University, Drug Management and Policy Kimura, Kazuko; Kanazawa University, Drug Management and Policy
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Global health, Pharmacology and therapeutics, Nutrition and metabolism
Keywords:	PUBLIC HEALTH, NUTRITION & DIETETICS, MEDICAL LAW, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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9 1 Public health concerns for anti-obesity medicines imported for  
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11 2 personal use through the Internet: a cross-sectional study  
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14 3 survey

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17 4 Mohiuddin Hussain Khan,<sup>1,\*</sup> Tsuyoshi Tanimoto,<sup>2</sup> Yoko Nakanishi,<sup>1,3</sup> Naoko Yoshida,<sup>1</sup> Hirohito

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37 12 **Running title:** Quality of online anti-obesity medicines

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40 13 **Word counts:** 3,996088

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42 14 **Key Words:** Quality, counterfeit medicine, public health, the Internet, anti-obesity

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9 17 **ABSTRACT**

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11 **Objectives:** To explore the circulation of anti-obesity medicines via the Internet and their  
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14 quality.

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17 **Design:** Cross-sectional study survey.

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20  
21 **Setting:** Internet pharmacies and pharmaceutical suppliers accessible from Japan.

22  
23 **Participants:** Anti-obesity medicines were purchased using relevant keywords on Japanese  
24  
25 Google search engine. Blogs and advertisement-only sites were excluded.

26  
27 **Primary and secondary outcome measures:** The authenticity of the samples was investigated  
28  
29 in collaboration with the manufacturers of the samples and medicine regulatory authorities. of  
30  
31 Quality of the samples were performed by pharmacopoeial analyses utilizing high performance  
32  
33 liquid chromatography.

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36  
37 **Results:** Eighty-two samples were purchased from 36 internet sites. Approximately half of the  
38  
39 sites did not mention a physical address, and 45% of the samples did not contain a package  
40  
41 insert. A variety of custom declarations were made for the shipments of the samples: personal  
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43 health items, supplement, medicines, general merchandise, tea and others. Among 82 samples,  
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46  
47 52 samples were analyzed to check their pharmacopoeial quality. Authenticity responses were  
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50 received from only five out of 20 manufacturing companies. According to pharmacopoeial  
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52 analyses and authenticity investigation, three of the samples were identified as counterfeits and  
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9 35 did not contain any active ingredients. ~~According to the chemical analyses,~~ Two of these  
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11 36 samples were confirmed as counterfeits by the manufacturer of the authentic products. The  
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14 37 manufacturer of the other sample did not respond to our request for an authenticity check even  
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16  
17 38 after several communication attempts. These counterfeit cases have been reported at the rapid  
18  
19 39 alert system of Western Pacific Region of the World Health Organization.

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21  
22 40 **Conclusion:** Many counterfeit and unapproved anti-obesity medicines may be easily bypassing  
23  
24 41 regulatory checks during shipping and are widely circulated through the Internet. Regulatory  
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27 42 authorities should take measures to prevent these medicines from entering countries to  
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29 43 safeguard their citizens.  
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9 52 **ARTICLE SUMMARY**

10  
11 53 **Article Focus**

- 12  
13  
14 • Quality of online anti-obesity medicines.  
15  
16  
17 55 • Circulation of unapproved anti-obesity medicines via the Internet.  
18

19 56 **Key Messages**

- 20  
21  
22 57 • Counterfeit and substandard anti-obesity medicines, orlistat are identified.  
23  
24 58 • False and vague custom declarations were made by some of the shipping  
25  
26  
27 59 companies to by-pass regulatory checks of unapproved online medicines.  
28

29 60 **Strengths and Limitations**

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31  
32 61 Small sample size and low authenticity response rate are limitations of this study.  
33  
34 62 However, the study provides valuable information for regulatory authorities on how  
35  
36  
37 63 unapproved and counterfeit medicines are being circulated through the Internet.  
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40 64 Concerted efforts of authentic manufacturers and medicine regulatory authorities are [a](#)  
41  
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43 65 must to combat counterfeits and ensure access of quality medicines to online consumers.  
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66 **INTRODUCTION**

67 Over the past decade, the Internet has become an integral part of life for a variety of uses. [A](#)  
68 [growing proportion](#) ~~Approximately 60%~~ of Internet users in some developed countries, [such as](#)  
69 [Japan and United States of America \(USA\)](#), utilize the Internet for their health related  
70 activities. [\[1-4\]\[1, 2\]](#) In fact, when Internet users were asked about specific searches related to  
71 health, such as diet and fitness information or health insurance materials, 80% of the users  
72 [among adult Americans](#) in a 2002 survey said that they had performed these types of  
73 searches. [\[1\]](#) According to a survey taken in Japan, a majority (86.3%) of the medicines imported  
74 for personal use were purchased through the Internet. [\[5\]\[3\]](#) However, according to World Health  
75 Organization (WHO), more than 50% of the medicines from Internet sites, which often conceal  
76 their physical address, may be counterfeit or of substandard quality. [\[6\]\[4\]](#)  
77 [WHO defines counterfeit medicines as ones which are deliberately and fraudulently mislabeled](#)  
78 [with respect to identity and/or source.\[7-9\] On the other hand, substandard medicines are](#)  
79 [legitimate ones that do not meet the quality specifications claimed by their manufacturers.\[10\]](#)  
80  
81 [A number of reports documented the severity of drug counterfeiting during the last two decades.](#)  
82 [WHO found that 20-90% of drugs were counterfeited in some African countries.\[11, 12\] In](#)  
83 [Tanzania, 12.2% of antimalarials were identified as substandard in 2005.\[13\] In 2009, 37% of](#)

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9 84 the samples did not meet standards in Nigeria.[14] Similar evidences were also reported in  
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11 85 Asia,[15-17] The unprecedented growth of the Internet accompanied with globalization of  
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14 86 commerce might have worsened the situation further.[18-20]

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17 87  
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19 88 Obesity is becoming a major public health epidemic in this century and is associated with an  
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22 89 increased risk for a number of health problems, such as hypertension, dyslipidemia, type 2  
23  
24 90 diabetes, and cardiovascular diseases.[21][5] The prevalence of obesity and its associated  
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27 91 conditions are increasingly affecting both developed and developing countries over the last few  
28  
29 92 decades.[22][6] Studies suggest that primarily adolescent and adult males are overweight or  
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32 93 obese in Japan.[23][7] Recommended strategies for managing weight and obesity include  
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35 94 lifestyle changes with appropriate dietary management and exercise. However, individuals with  
36  
37 95 an isolated BMI $\geq 30$  kg m<sup>-2</sup> or a BMI $> 27$  kg m<sup>-2</sup> with co-morbidities such as type 2 diabetes,  
38  
39  
40 96 cardiovascular diseases, and obstructive sleep apnea, should receive pharmacotherapy as  
41  
42 97 well.[24][8] Among the available anti-obesity medicines, phentermine, diethylpropion and  
43  
44  
45 98 orlistat are approved by the U.S. Food and Drug Administration, but sibutramine has been  
46  
47 99 withdrawn from the market.[25, 26][9, 10] Of these anti-obesity medicines, only mazindol has  
48  
49  
50 100 been approved for use in Japan.[27][11] However, several of these anti-obesity medicines are  
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53 101 among those that are frequently imported into Japan for personal use.[28][12] Safety profile.

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9 102 risk vs benefit, cost-effectiveness of the investment deters manufacturers and marketers to get  
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11 103 interested in approving anti-obesity medicines for Japanese market.[29]  
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16  
17 105 The online purchase of medicine through the Internet is a growing and convenient practice for  
18  
19 106 many consumers. This practice has also become one of the most popular, easiest and safest

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21  
22 107 routes for counterfeit medicine traders.[6, 30-32][4, 13-15] The availability of counterfeit

23  
24 108 erectile dysfunction (ED) medicines had been reported in Japan by a limited number of case

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26 109 investigations.[33, 34] In addition, a joint investigation done by four pharmaceutical industries

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29 110 in Japan reported that approximately 60% of ED medicines available in the Internet are

30  
31 111 counterfeited.[34] However, the quality of anti-obesity and diet medicines available through the

32  
33 112 Internet in Japan was still unknown. Since, all types of therapeutic classes of medicines are

34  
35 113 counterfeited from essential medicines to lifestyle drugs, Because lifestyle medicines are

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37 114 frequently targeted by counterfeiters, a collaborative investigation between ~~the Ministry of~~

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39 115 ~~Health and Labour Welfare (MHLW), Japan;~~ Kanazawa University, Kanazawa; and Doshisha

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42 116 Women's College, Kyoto, Japan was conducted to survey the quality of anti-obesity medicines

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45 117 that were purchased through online medicine sites. This investigation also provided an

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48 118 understanding of the process by which unapproved medicines are being imported for and used

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51 119 by consumers in Japan.  
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14 122 **METHODS**15  
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17 123 **Study design**18  
19 124 Quality of online anti-obesity medicines was assessed using an online cross-sectional  
20  
21  
22 125 ~~study survey~~ during August 2009.  
23

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27 127 **Selection of Internet sites and sample collection**28  
29 128 ~~Internet sites were selected in five steps to purchase anti-obesity medicines. In the first step,~~30  
31  
32 129 ~~The Japanese keywords personal import agent (個人輸入代行), diet (ダイエット), and~~33  
34 130 ~~anti-obesity (肥満) medicines were used on the Japanese Google search engine~~35  
36  
37 131 ~~(www.google.co.jp). From a list of more than 140,000 results, first 500 were further screened~~38  
39  
40 132 ~~out to find online pharmacies or suppliers or brokers—that offer anti-obesity medicines~~41  
42 133 ~~provided that they did not mention their physical address in their websites. That means sites~~43  
44 134 ~~with physical address and/or blogs and advertise-only sites were excluded in this step. In the~~45  
46  
47 135 ~~second through fourth steps. Searches were also made on websites that advertise and sell~~48  
49  
50 136 ~~counterfeit Cialis (シアリス), Levitra (レビトラ) and Viagra (バイアグラ). The physical~~51  
52  
53 137 ~~characteristics of original and counterfeit Cialis and Levitra were both identified earlier by the~~  
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9 138 ~~Ministry of Health, Japan, and information on websites that sell counterfeit Viagra was provided~~  
10  
11 139 ~~by Pfizer.[16] As such, in the second step, the Japanese key words personal import agent (‘個人~~  
12  
13  
14 140 ~~輸入代行’), Cialis (‘シアリス’), ‘50mg’ and ‘100mg’ were used and first 100~~  
15  
16  
17 141 ~~results were further screened out from a list of more than 35,000 results to find out~~  
18  
19 142 ~~availability of anti-obesity medicines offered along side ED medicines. In the third step, key~~  
20  
21  
22 143 ~~words personal import agent (‘個人輸入代行’), Levitra (‘レビトラ’), ‘50mg’ and~~  
23  
24 144 ~~‘100mg’ were used and again first 100 results were screened out from a list of around~~  
25  
26  
27 145 ~~60,000 results. The physical characteristics (e.g.: color of genuine and counterfeits, strength,~~  
28  
29  
30 146 ~~packaging etc.) of original and counterfeit Cialis and Levitra were both identified earlier by the~~  
31  
32 147 ~~Ministry of Health, Japan.[33] In the fourth step, samples were purchased from nine internet~~  
33  
34 148 ~~sites where counterfeit Viagra (バイアグラ) was offered in the past and information on these~~  
35  
36  
37 149 ~~sites was provided by Pfizer. Finally, based on the information available from our previous~~  
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39  
40 150 ~~research, we searched homepages of ten domestic brokers and four of them were selected~~  
41  
42 151 ~~for sampling.~~

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45 152  
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47 153 After the exclusion of blogs and advertisement-only sites, 36 sites were chosen in total for the  
48  
49  
50 154 purchase of anti-obesity medicines. ~~Some of the criteria used in choosing the sites included the~~  
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53 155 ~~absence of a physical address and the presence of suspicious advertisements.~~ A list of

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9 156 overweight/anti-obesity medicines was sought on each of the selected sites. ~~Priority rankings~~  
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11 157 ~~were made of the list of Available medicines in the lists were numbered consecutively~~ according  
12  
13  
14 158 to their vertical or horizontal placement on the web pages, ~~excluding foods and drinks items.~~  
15  
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17 159 Samples of the anti-obesity medicines were purchased from selected sites according to the  
18  
19 160 smallest ~~priority~~ number found for a medicine that had not been purchased from a previous  
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22 161 website.

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24 162  
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27 163 Information on the site's name, URL, compliance with Japanese rules of "Act on Specified  
28  
29 164 Commercial Transaction" (ASCT), e-mail address, the name of the product and other  
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31  
32 165 information such as the dosage, efficacy and side effects, recommendation on consultation with  
33  
34 166 doctors or pharmacists or opportunities for consultation were recorded while examining the sites  
35  
36  
37 167 from which at least one product was purchased. ~~ASCT is the policy guidelines of all kinds of~~  
38  
39 168 ~~business transaction in Japan to protect the interests of consumers. These guidelines cover~~  
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41  
42 169 ~~door-to-door sales, mail order sales, telemarketing etc. According to the ASCT all e-commerce~~  
43  
44  
45 170 ~~sites in Japan should mention their name, address(es), telephone numbers of the~~  
46  
47 171 ~~suppliers/brokers, prices of offered for commodities, shipment procedure(s) etc. in their~~  
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50 172 ~~advertisements.[35]~~

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9 174 **Observational analysis**

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11 175 All of the samples were given distinct codes when the shipments were received. The name of  
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14 176 the product, dosage form, content information from the printed label, the manufacturers' name  
15  
16  
17 177 and address, the country of origin, the manufacture and expiration dates, lot, registration and  
18  
19 178 license numbers, presence of package insert and their languages, Japanese ~~manual~~,  
20  
21  
22 179 information/notes, information from the shipping company, the sending country, the date of  
23  
24 180 shipment and arrival, and customs declaration notations were recorded for each of the samples.  
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27 181

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29 182 **Chemical analysis**

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31  
32 183 Pharmacopoeial procedures for the analysis of the samples (i.e.: orlistat, sibutramine,  
33  
34 184 rimonabant, benfluorex and lovastatin) were established and performed using high performance  
35  
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37 185 liquid chromatography (HPLC), which are described briefly below. However, analytical  
38  
39  
40 186 methods and results of rhei rhubarb and herbal products (i.e.: pahyma hoelen, ophiopogonis  
41  
42 187 tuber and dai dai hua) were excluded, since they will be reported elsewhere.  
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47 189 Preparation of the sample solutions

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50 190 Randomly selected capsules of orlistat and sibutramine samples were weighed accurately. After  
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53 191 each capsule was weighed, the contents were removed, and the empty capsule shells were  
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9 192 subsequently weighed. The difference between the weight of the whole capsule and the capsule  
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11 193 shell was assumed to be the weight of the contents. To prepare sample solutions of lovastatin,  
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13 194 benfluorex and rimonabant tablets, randomly chosen tablets were weighed accurately and  
14  
15 195 subsequently crushed separately into powder. Approximately 80 ml of methanol was added to  
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17 196 the capsule's contents or tablet powder, and the mixture was sonicated for 30 min. After  
18  
19 197 sonication, methanol was then added to a volume of 100 ml. The resulting solutions were  
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21 198 filtered through a membrane filter (pore size: 0.45  $\mu\text{m}$ ) and used as the sample solutions.  
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27 199  
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29 200 ~~To prepare sample solutions of lovastatin, benfluorex and rimonabant tablets, randomly chosen~~  
30  
31 201 ~~tablets were weighed accurately and subsequently crushed separately into powder.~~  
32  
33 202 ~~Approximately 80 ml of methanol was added to the powder, and the solutions were sonicated~~  
34  
35 203 ~~for 30 min. Methanol was added to each of the solutions to a volume of 100 ml. The resulting~~  
36  
37 204 ~~solutions were filtered through membrane filters (pore size: 0.45  $\mu\text{m}$ ) and used as the sample~~  
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39 205 ~~solutions.~~  
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47 207 Preparation of standard solutions

48  
49 208 Three consecutive strengths of standard solutions were prepared by dissolving 0.375 mg, 0.75  
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51 209 mg and 1.50 mg of orlistat; 0.050 mg, 0.100 mg and 0.200 mg of sibutramine; 0.100 mg, 0.200  
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9 210 mg and 0.500 mg of lovastatin; 0.100 mg, 1.50 mg and 2.00 mg of benfluorex; 0.100 mg, 0.200  
10  
11 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.

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17 213 Assay condition

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19 214 Ten microliters of each sample solution and standard solution was placed in vials and assayed

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21 215 using a photodiode array of 225 nm wavelength (200–400 nm range for spectra) with a stainless

22  
23  
24 216 steel column with a 4.6 mm internal diameter and 15 cm length packed with octadecylsilanized

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27 217 silica gel for liquid chromatography (5 µm particle diameter) used with Mightysil RP-18 GP

28  
29 218 150-4.6. The column temperature was maintained at 45°C. A mixture of methanol and phosphate

30  
31  
32 219 buffer, pH 7.0 (17:3) was used as the mobile phase at a flow rate of 1.2 ml/min.

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36  
37 221 **Authenticity investigation**

38  
39 222 A catalogue and a questionnaire for all the samples were created that included the information

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41  
42 223 from the printed labels of the product packages. The printed information was also checked

43  
44 224 against the information on the manufacturers' websites. The questionnaires were sent to the

45  
46  
47 225 appropriate manufacturers with a portion of the samples for verification of their authenticity.

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49  
50 226 The regulatory authorities for medicine in the country of origin were also contacted to verify the

51  
52  
53 227 legitimacy of the products and their approval for marketing. After considering the WHO



228 definition of counterfeit medicines, the gathered information was analyzed to determine the  
 229 authenticity of the individual samples and their manufacturers.<sup>[7, 36][17, 18]</sup>

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231 **Statistical analysis**

232 Because of the small size of the sample, descriptive statistical analysis was performed using  
 233 Microsoft Excel.

235 **RESULTS**

236 A total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet  
 237 sites (Table 1). On average, these sites offered 62 kinds of products (including diet foods and  
 238 drinks). Some of these products were shipped in divided shipments and treated as distinct  
 239 samples. Of the selected internet sites, 15 sites did not show a physical address, and six, two and  
 240 nine of the web sites advertised counterfeit Cialis, Levitra and Viagra, respectively. Two of the  
 241 sites with fake Cialis and Viagra also did not show a physical address. Four of the websites were  
 242 hosted by domestic shipping companies.

244 Table 1. Active Ingredient

<u>Active Ingredient</u>	<u>Approval status in Japan</u>	<u>n(%)</u>	<u>Classification</u>
<u>Sibutramine hydrochloride</u>	<u>Not approved</u>	<u>42 (51.2)</u>	<u>Prescription medicine</u>

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<u>Orlistat</u>	<u>Not approved</u>	<u>15 (18.3)</u>	<u>Prescription medicine: 10</u> <u>Over the counter: 5*</u>
<u>Rimonabant</u>	<u>Not approved</u>	<u>2 (2.4)</u>	<u>Prescription medicine</u>
<u>Benfluorex</u>	<u>Not approved</u>	<u>2 (2.4)</u>	<u>Prescription medicine</u>
<u>Lovastatin**</u>	<u>Not approved</u>	<u>2 (2.4)</u>	<u>Prescription medicine</u>
<u>Pachyma hoelen (茯苓)</u>	<u>Approved</u>	<u>14 (17.1)</u>	<u>Over the counter</u>
<u>Ophiopogonis tuber (麦門冬)</u>	<u>Approved</u>	<u>3 (3.6)</u>	<u>Over the counter</u>
<u>Rhei Rhubarb (大黄)**</u>	<u>Approved</u>	<u>1 (1.2)</u>	<u>Over the counter</u>
<u>Dai dai hua (代代花)</u>	<u>Approved</u>	<u>1 (1.2)</u>	<u>Over the counter</u>
<u>Total</u>		<u>82 (100.0)</u>	

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245 \*: Alli (orlistat 60 mg), \*\*: Not classified as anti-obesity medicines, available under diet (ダイ  
 246 エット) search

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#### 248 Information available on the web sites

249 Different levels of compliance with ASCT were observed throughout all (36) of the web  
 250 sites.<sup>[35]</sup> For instance, all (100%) of them mentioned the selling price, shipping charges for the  
 251 goods, and methods of payment. However, only 21 (58.3%) of them provided telephone  
 252 numbers, and only 17 (47.2%) of them mentioned a physical address.

253

254 Information for e-mail addresses and shipment procedures were presented on all of the selected  
 255 sites. However, only 21 (58.3%) of them encouraged consumers to consult with a physician or  
 256 pharmacist. Consultation services were available at two (5.5%) of the sites. Dosage and  
 257 administration, effects and efficacy, and side effects related to the products were explained in 18  
 258 (50%), 23 (63.8%) and 17 (47.2%) of the sites, respectively, despite the prohibition on

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9 259 advertisements for unapproved medicines.

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14 261 **Information provided with the samples**

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16 262 Upon examination of the printed materials, the languages of the package inserts were found to

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19 263 be in English for 14 (17.1%) of the samples, Chinese for 13 (15.9%), both Chinese and Korean

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22 264 for 10 (12.2%), both English and Chinese for 4 (4.9%), Turkish for 2 (2.4%), both English and

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24 265 Thai for 1 (1.2%), and English, Chinese and Russian for 1 (1.2%) of the samples. However, 37

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26 266 (45.1%-(37)) of the samples did not have any package inserts.

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32 268 **Shipment of the samples**

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34 269 Samples were sent by 29 different shipping companies. The majority (13 companies) shipped

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37 270 from China, and the second largest group was from India (4 companies). Others were shipped

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40 271 from the USA (3), Japan (2), Thailand (2), Switzerland (1), Hong Kong (1), Cambodia (1), the

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42 272 Fiji Islands (1), and Puerto Rico (1). The customs declaration was 'health product/personal

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44 273 health items' for 20 (24.4%) of the samples, 'supplement' for 13 (15.9%) of the samples,

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46 274 'medicine' for 10 (12.2%) of the samples and the actual name of the product in 2 (2.4%) cases.

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49 275 However, 12 (14.7%) of the samples were shipped with a declaration of general merchandise

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52 276 and/or tea, 11 (13.4%) of them declared 'other' and 14 (17.1%) of them did not mention

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9 277 anything as the declaration. Interestingly, one representative from an importing agent of a diet  
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11 278 medicine clinic (Sabairato Yanhee MD and clinic, <http://www.gop23.com>) inquired over the  
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14 279 telephone regarding the purpose for our purchase of the medicine and asked if we had any  
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17 280 relationship with the MHLW, Japan; they did not sell their products to us.  
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### 282 **Sample characteristics**

283 Of the 82 samples, ~~423~~ (512.24%) were advertised on the websites as containing sibutramine  
284 hydrochloride and 15 (18.3%) were advertised as orlistat. Rimonabant, benfluorex, and  
285 lovastatin were advertised to be in two (2.4%) of the samples. Rhei rhubarb was said to be in  
286 one, and the remaining ~~187~~ (210.97%) samples were advertised to be herbal products (Table 1).  
287 All these products were advertised by their brand names. The results of the rhubarb and herbal  
288 products will be reported elsewhere. Out of the 64 synthetic products, 58 samples from 19  
289 different products were prescription medicines, however, none of which requested a prescription  
290 for the purchase. Five brands of orlistat were over-the-counter medicines, and one sample,  
291 Daidai hua, was marketed as a natural supplement. Interestingly, daidai hua ~~However, this~~  
292 ~~product~~ was advertised as sibutramine by its agent, and the sample actually contained  
293 sibutramine as shown by chemical analysis. According to purported country of marketing  
294 authorization holder, 25 sibutramine products originated from India (dispatched from India,

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9 295 Hong Kong and Fiji Islands), seven from China (dispatched from China), seven from Germany  
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11 296 (dispatched from Hong Kong and Cambodia) and three from Hong Kong (dispatched from  
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14 297 Cambodia). Among 15 orlistat products, seven originated from India (dispatched from India and  
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16 298 Japan), five from United Kingdom (dispatched from Switzerland, USA and Japan), two from  
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19 299 Switzerland (dispatched from Puerto Rico) and one from Thailand (dispatched from Thailand).  
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22 300 Two rimonabant, benfluorex and one lovastatin samples originated from India (dispatched from  
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24 301 Thailand and Japan), France (dispatched from Hong Kong) and USA (dispatched from USA)  
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26  
27 302 respectively. All herbal products (including daidai hua) originated from China, except two (i.e.:  
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29 303 Pachyma hoelen), which are from USA, however, dispatched from China.  
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#### 305 **Quality analysis**

306 Out of total, 52 samples (i.e.: Sibutramine: 21, Orlistat: 13, Rimonabant: 2, Benfluorex: 2,  
307 Lovastatin: 1 and herbal products: 13) were analyzed by HPLC to measure quantity of active  
308 ingredients in the samples. Thirty samples were excluded because of the insufficient materials.

309 Quantitative analysis by HPLC showed that all (21) of the samples of sibutramine were in the  
310 acceptable range (90%-110%) except one (mean content percentage of 60.2±7.6). No active  
311 ingredient was detected in three out of the 13 samples of orlistat that we tested (Figure 1). These  
312 three samples were identified to be counterfeit. Of these three counterfeit samples, two were

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9 313 found to be Xenical after analysis by the researchers and the manufacturer of the genuine  
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11 314 products. No active ingredient was detected in the last sample, only starch (Figure 1). The other  
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13 315 counterfeit sample contained unknown excipients. None of the samples of lovastatin, benfluorex  
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16 316 or rimonabant failed the HPLC analysis.  
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### 21 318 **Authenticity investigation**

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24 319 Responses to our requests for authentication were received from only five of the 20  
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26 320 manufacturing companies of the genuine samples. According to the responses that we received,  
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29 321 all of the responding manufacturers were GMP compliant. Of the 12 reported samples, two of  
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32 322 the orlistat samples (Xenical) from the same manufacturer were confirmed to be counterfeit  
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34 323 (Table 24).  
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47 328 Table 24. Results of Authenticity Investigation

Active ingredient	Labeled cCountry of Authorized mMarketing	Genuine sample	Counterfeit sample	Manufacturing License

<u>authorization holder*</u>				
Orlistat (60 mg)	USA	5	0	YES
Benfluorex (150 mg)	France	2	0	YES
Rimonabant (20 mg)	India	1	0	YES
Orlistat (120 mg)	Switzerland	1	2	YES
Rhei Rhubarb	China	1	0	YES
*Orlistat (120 mg)	India	0	1	Unknown

329 \* labeled manufacturer did not reply

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331 The counterfeit samples were purchased at [www.kenkoclinic.com](http://www.kenkoclinic.com) and sent to us from Puerto

332 Rico. They bore the same manufacture and expiration dates (MFD: 02/2011 and EXP: 02/2011,

333 Figure 2) on their blisters, which had not yet occurred at the time of our investigation. The

334 printed information on the blisters of the counterfeits was a different color with a similar but

335 slightly different logo (Figure 3).

336

337 Telephone communications were made to the manufacturer of Zenigal (orlistat 120 mg) in India,

338 which did not contain any of the active ingredients that had been claimed on the product labels.

339 However, the manufacturer did not respond after several communication attempts. This

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9 340 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of  
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11 341 counterfeit medicines at the rapid alert system of the Western Pacific Region of the World  
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14 342 Health Organization.

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19 344 Responses were received from the medical regulatory authorities of three countries (Germany,  
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21 345 Switzerland and USA) for five of the manufacturers. Their responses stated that only orlistat has  
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23 346 approval to be manufactured in Switzerland. Approval for the manufacture of sibutramine in  
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27 347 Germany was suspended in January 2010, and it was not approved for use in the USA.

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## 31 32 349 **DISCUSSION**

### 33 34 350 **Provided information on the samples**

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37 351 According to the Pharmaceutical Affairs Law in Japan, advertising of unapproved medicines is  
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39 352 prohibited, and Customs should seize any shipment of prescription medicines when the amount  
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42 353 exceeds more than a one-month dose or any non-prescription medicines that exceed more than a  
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45 354 two-month dose. However, at least some of the samples in this study that exceeded the approved  
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47 355 amount for shipment made it through the regulatory checks during shipping.<sup>[37][19]</sup>

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50 356 Surprisingly, at least four of the shipping companies are conducting business in Japan. Contact  
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53 357 information was not provided on many of the sites (52.8%), which seemingly contradicts  
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9 358 ASCT,<sup>[35][20]</sup> According to our study, nearly fifty percent of the sites mentioned dosage  
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11 359 administration, effects or side-effects of the medicines, which are not permitted by the  
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13 360 pharmaceutical affairs laws (PAL) in Japan.<sup>[37][19]</sup> As found in many previous studies on  
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16 361 e-medicines, approximately 50% of the samples did not contain a package insert.<sup>[38-42][21-25]</sup>  
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19 362 Moreover, several of the weight-loss products may contain harmful or contraindicated  
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21 363 ingredients.<sup>[33, 38][16, 21]</sup> Similar to the findings of a recent study, none of the websites of our  
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24 364 study required a prescription to purchase medicines.<sup>[43, 44]</sup>  
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### 366 Approval status of the products

32 367 The majority of the study samples were sibutramine, which is a selective inhibitor of the central  
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34 368 neuronal reuptake of serotonin and noradrenaline and reduces food intake and body  
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37 369 weight.<sup>[45][26]</sup> However, after conclusion of the safety review of sibutramine, the European  
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40 370 Medicines Agency (EMA) has suspended its marketing authorization in the European Union  
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42 371 (EU).<sup>[46][27]</sup> A recently published study reported that generic Figurer (sibutramine 10 mg),  
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45 372 even though it has not been reviewed by the responsible government (USA, the exporting  
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47 373 nation), is freely circulating via the Internet, which is a serious concern for public  
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50 374 health.<sup>[39][22]</sup> According to the medicine regulations of Hong Kong, Figurer does not need  
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53 375 manufacturing authorization because the medicine is manufactured in a foreign country. The  
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9 376 authorization status of Ali (orlistat 60 mg) as a prescription medicine has been recommended to  
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11 377 transition to a non-prescription medicine in the EU.~~[47][28]~~ In a questionnaire conducted by  
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13 378 community pharmacists in Great Britain, orlistat is suspected to be misused by consumers, as  
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15 379 stated in their responses.~~[48][29]~~ Similarly, marketing authorization for Acomplia (rimonabant)  
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17 380 has also been withdrawn in the EU in January 2009 and safety profiles of other anti-obesity  
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19 381 agents are generating controversy in different parts of the world.~~[49-53][30-33]~~ Even though all  
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21 382 the anti-obesity agents sampled in this survey are unapproved in Japan, it is possible that anyone  
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23 383 can procure these items without declaring the actual contents during shipping.  
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### 385 **Authenticity and quality of the samples**

386 As similarly shown in previous studies, we observed low rates of authenticity.~~[54][34]~~  
387 Responses from only five (25%) of the manufacturers for 14.6% of the samples were received.  
388 The counterfeit samples identified in this survey were confirmed by the manufacturer of the  
389 corresponding genuine products. Counterfeiting of anti-obesity medicines, particularly orlistat,  
390 has been previously reported.~~[55, 56][35, 36]~~ Based on the external characteristics of the  
391 counterfeits, these products most often differ in their printed information, design, color, etc.  
392 from those of the genuine drugs.~~[17, 57][37, 38]~~ As shown in some other studies, the  
393 counterfeits detected in this survey did not contain any active ingredients.~~[54, 58][34, 39]~~ It is

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394 not clear why the manufacture of Zenigal, which failed the content analysis, did not respond to  
395 our authentication request. In such a case, it can be assumed that the manufacturer is already  
396 aware of the distribution of low-quality products in the pharmaceutical market. Several reports  
397 suggest that patients have sought medical treatment for life-threatening complications after the  
398 consumption of fake or substandard medicines purchased online.<sup>[59][40]</sup> When products are  
399 purchased through the Internet and the sites are not sufficiently regulated, customers are left to  
400 accept the consequences.

402 According to Japanese PAL, a person violating pharmaceutical regulation may be sentenced to  
403 an imprisonment of up to 3 years or imposed a penalty of up to JP¥ 3 million or both.<sup>[60]</sup> In  
404 case of such violation by a company, the penalty may be increased to maximum JP¥ 100  
405 million.<sup>[60]</sup> Nevertheless, PAL has only jurisdiction to regulate domestic traders and has no  
406 hold on foreign online traders. Strengthening international collaboration along with  
407 public-private partnership initiatives may facilitate stemming out illegal internet trading hosted  
408 from outside national boundaries.<sup>[19, 61, 62]</sup>

410 One of the limitations of the study might be small sample size, which may restrict study  
411 findings to Japan. The sampling scheme may also limit our findings from generalization to all

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9 412 internet sites. However, the sampling scheme was purposefully designed to investigate  
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11 413 suspicious online medicine sites. Our study was not designed comprehensively to explore  
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14 414 information during shipment of medicinal products especially at Japanese custom check.  
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16 415 Further evaluation with a representative sample may provide more information on the extent of  
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19 416 the problem. Low response rate of authenticity investigation may also be considered as a  
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22 417 limiting factor. However, better communication and cooperation among authentic manufacturers  
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25 418 and medicine regulatory authorities may increase response rate and generate more information  
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27 419 to counteract against counterfeits.  
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## 31 421 **CONCLUSIONS**

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34 422 It is evident from this study that counterfeit, unapproved and suspended anti-obesity medicines  
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37 423 are circulating via the Internet. Because of gaps and the insufficient monitoring system of  
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40 424 imports for personal use in the rapidly growing e-commerce environment, these medicines can  
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43 425 easily enter into the distribution channels for pharmaceuticals and may pose health hazards for  
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45 426 consumers. Time has come to address such gaps of cross-border pharmaceutical e-commerce  
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47 427 and to regulate through international cooperation and public-private partnerships. Obviously,  
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50 428 first and foremost step should be at country levels to make necessary amendments of existing  
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53 429 regulation focusing online pharmaceutical transactions. Side by side, there might be an urgent  
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9 430 [need at international level to formulate common regulation and agreements focusing issues of](#)  
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11 431 [pharmaceutical e-commerce.](#)  
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19 434 **Acknowledgements** We gratefully acknowledge the cooperation received from the staff of  
20  
21 435 MHLW. Additionally, we thank Ms. Hitomi Tabata for her cooperation in this work.  
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27 437 **Funding** This study was supported by Health and Labour Sciences Research Grants from the  
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29 438 MHLW, Japan.  
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34 440 **Competing interests** The authors declare no conflict of interest.  
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42 443 **Authors' contribution** MHK, TT, YN, and KK participated in the conception and design of the  
43  
44 444 study; TT, YN and KK participated in sampling activities and analysis of the samples; MHK, TT,  
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46 445 YN, NY, HT and KK participated in data analysis and interpretation of results. MHK wrote the  
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48 446 first draft of the manuscript. All authors contributed in the critical review of the draft manuscript,  
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50 447 editing and finally approved its submitted version.  
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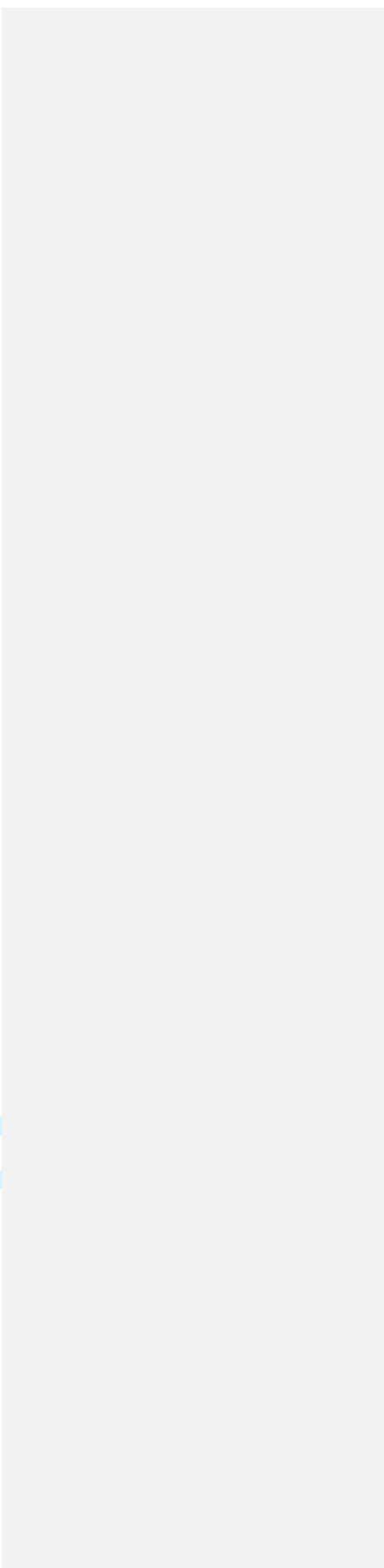
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449 **Data sharing statement** No additional data available.

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For peer review only



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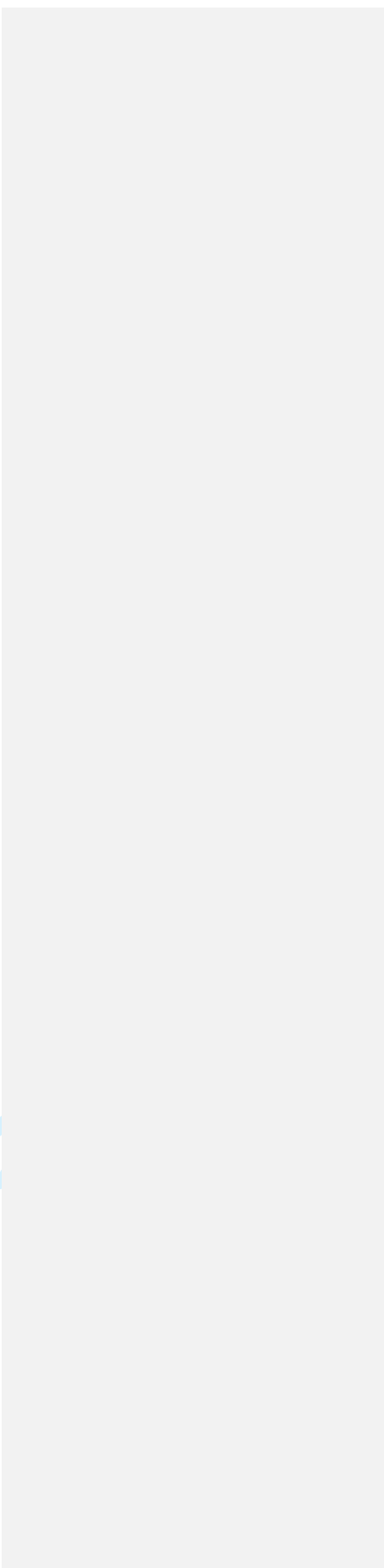
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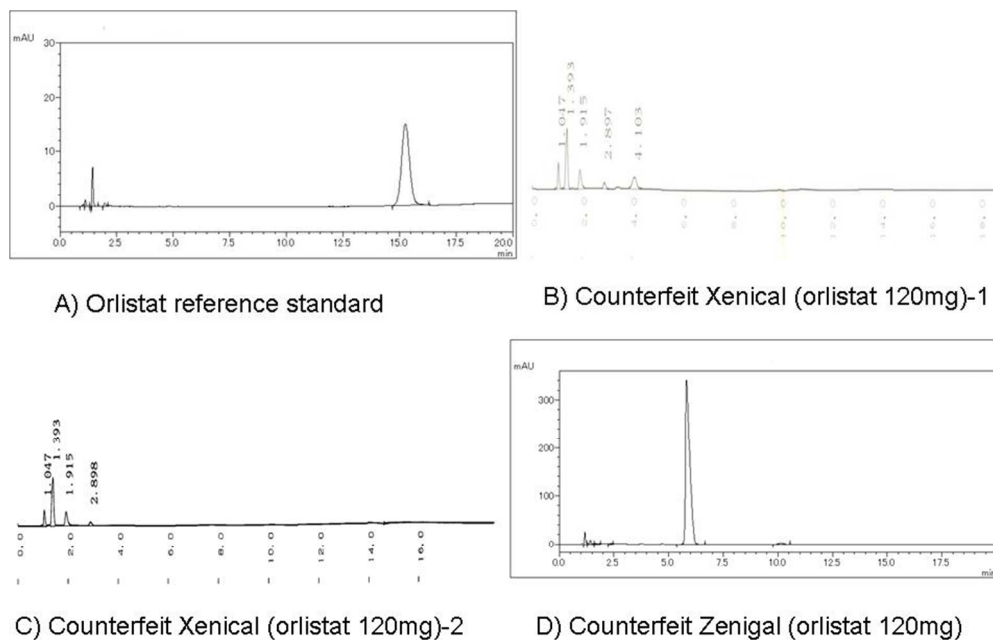


Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples  
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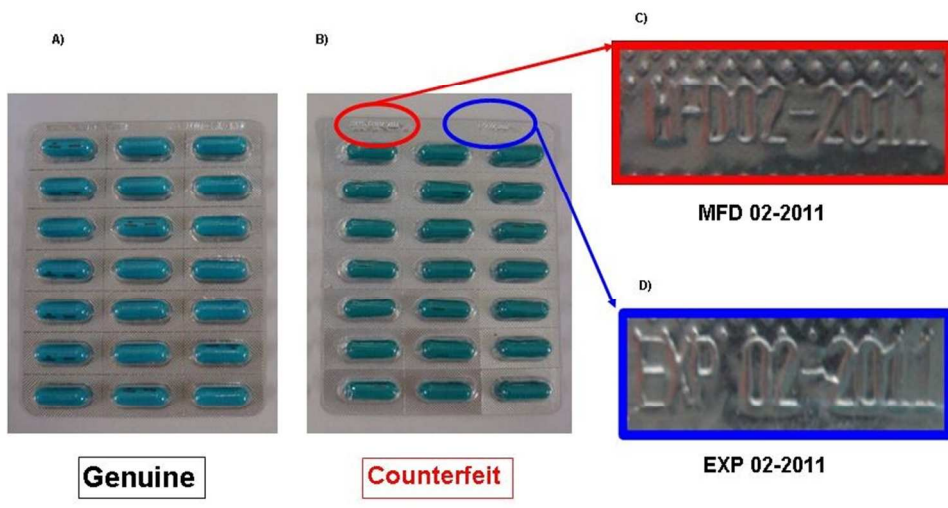


Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)  
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Figure 3. Reverse side of blister: A) Logo of genuine sample, B) Logo of counterfeit sample  
254x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	N.A.
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	N.A.
		(c) Explain how missing data were addressed	N.A.
		(d) If applicable, describe analytical methods taking account of sampling strategy	N.A.
		(e) Describe any sensitivity analyses	N.A.
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13
		(b) Give reasons for non-participation at each stage	11-13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14
		(b) Indicate number of participants with missing data for each variable of interest	13-14
Outcome data	15*	Report numbers of outcome events or summary measures	14-16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N.A.
		(b) Report category boundaries when continuous variables were categorized	N.A.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	17-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



**Public health concerns for anti-obesity medicines imported for personal use through the Internet: a cross-sectional study**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-000854.R2
Article Type:	Research
Date Submitted by the Author:	05-Apr-2012
Complete List of Authors:	Khan, Mohiuddin; Kanazawa University, Drug Management and Policy Tanimoto, Tsuyoshi; Doshisha Women's College, Nakanishi, Yoko; Public Health Center, ; Kanazawa University, Drug Management and Policy Yoshida, Naoko; Kanazawa University, Drug Management and Policy Tsuboi, Hirohito; Kanazawa University, Drug Management and Policy Kimura, Kazuko; Kanazawa University, Drug Management and Policy
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Global health, Pharmacology and therapeutics, Nutrition and metabolism
Keywords:	PUBLIC HEALTH, NUTRITION & DIETETICS, MEDICAL LAW, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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9 1 Public health concerns for anti-obesity medicines imported for  
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17 4 Mohiuddin Hussain Khan,<sup>1,\*</sup> Tsuyoshi Tanimoto,<sup>2</sup> Yoko Nakanishi,<sup>1,3</sup> Naoko Yoshida,<sup>1</sup> Hirohito  
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19 5 Tsuboi,<sup>1</sup> Kazuko Kimura,<sup>1</sup>

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29 9 \* **Corresponding author:** Drug Management and Policy, Kanazawa University, Kakuma-machi,

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37 12 **Running title:** Quality of online anti-obesity medicines

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40 13 **Word counts:** 3,392,088

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42 14 **Key Words:** Quality, counterfeit medicine, public health, the Internet, anti-obesity

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17 **ABSTRACT**

18 **Objectives:** To explore the circulation of anti-obesity medicines via the Internet and their  
19 quality.

20 **Design:** Cross-sectional study survey.

21 **Setting:** Internet pharmacies and pharmaceutical suppliers accessible from Japan.

22 **Participants:** Anti-obesity medicines were purchased using relevant keywords on Japanese  
23 Google search engine. Blogs and advertisement-only sites were excluded.

24 **Primary and secondary outcome measures:** The authenticity of the samples was investigated  
25 in collaboration with the manufacturers of the samples and medicine regulatory authorities. of  
26 Quality of the samples were performed by pharmacopoeial analyses utilizing high performance  
27 liquid chromatography.

28 **Results:** Eighty-two samples were purchased from 36 internet sites. Approximately half of the  
29 sites did not mention a physical address, and 45% of the samples did not contain a package  
30 insert. A variety of custom declarations were made for the shipments of the samples: personal  
31 health items, supplement, medicines, general merchandise, tea and others. Among 82 samples,  
32 52 samples were analyzed to check their pharmacopoeial quality. Authenticity responses were  
33 received from only five out of 20 manufacturing companies. According to pharmacopoeial  
34 analyses and authenticity investigation, three of the samples were identified as counterfeits and



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9 35 did not contain any active ingredients. ~~According to the chemical analyses,~~ Two of these  
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11 36 samples were confirmed as counterfeits by the manufacturer of the authentic products. The  
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14 37 manufacturer of the other sample did not respond to our request for an authenticity check even  
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17 38 after several communication attempts. These counterfeit cases have been reported at the rapid  
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19 39 alert system of Western Pacific Region of the World Health Organization.

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22 40 **Conclusion:** Many counterfeit and unapproved anti-obesity medicines may be easily bypassing  
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24 41 regulatory checks during shipping and are widely circulated through the Internet. Regulatory  
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27 42 authorities should take measures to prevent these medicines from entering countries to  
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29 43 safeguard their citizens.

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9 52 **ARTICLE SUMMARY**

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11 53 **Article Focus**

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14 • Quality of online anti-obesity medicines.  
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17 55 • Circulation of unapproved anti-obesity medicines via the Internet.  
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19 56 **Key Messages**

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22 57 • Counterfeit and substandard anti-obesity medicines, orlistat are identified.  
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24 58 • False and vague custom declarations were made by some of the shipping  
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27 59 companies to by-pass regulatory checks of unapproved online medicines.  
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29 60 **Strengths and Limitations**

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32 61 Small sample size and low authenticity response rate are limitations of this study.  
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34 62 However, the study provides valuable information for regulatory authorities on how  
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37 63 unapproved and counterfeit medicines are being circulated through the Internet.  
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40 64 Concerted efforts of authentic manufacturers and medicine regulatory authorities are a  
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43 65 must to combat counterfeits and ensure access of quality medicines to online consumers.  
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## 66 INTRODUCTION

67 Over the past decade, the Internet has become an integral part of life for a variety of uses.

68 Approximately 60% of Internet users in some developed countries, such as Japan and United

69 States of America (USA), utilize the Internet for their health related activities, [1-4][1, 2] In fact,

70 when Internet users were asked about specific searches related to health, such as diet and fitness

71 information or health insurance materials, 80% of the users among adult Americans in a 2002

72 survey said that they had performed these types of searches, [1] According to a survey taken in

73 Japan, a majority (86.3%) of the medicines imported for personal use were purchased through

74 the Internet, [5][3] However, according to World Health Organization (WHO), more than 50% of

75 the medicines from Internet sites, which often conceal their physical address, may be counterfeit

76 or of substandard quality, [6][4]

77 WHO defines counterfeit medicines as ones which are deliberately and fraudulently mislabeled

78 with respect to identity and/or source.[7-9] On the other hand, substandard medicines are

79 legitimate ones that do not meet the quality specifications claimed by their manufacturers.[10]

80

81 A number of reports documented the severity of drug counterfeiting during the last two decades.

82 WHO found that 20-90% of drugs were counterfeited in some African countries.[11, 12] In

83 Tanzania, 12.2% of antimalarials were identified as substandard in 2005.[13] In 2009, 37% of

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9 84 the samples did not meet standards in Nigeria.[14] Similar evidences were also reported in  
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11 85 Asia.[15-17] The unprecedented growth of the Internet accompanied with globalization of  
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14 86 e-commerce might have worsened the situation further.[18-20]  
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19 88 Obesity is becoming a major public health epidemic in this century and is associated with an  
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22 89 increased risk for a number of health problems, such as hypertension, dyslipidemia, type 2  
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24 90 diabetes, and cardiovascular diseases.[21][5] The prevalence of obesity and its associated

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27 91 conditions are increasingly affecting both developed and developing countries over the last few  
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29 92 decades.[22][6] Studies suggest that primarily adolescent and adult males are overweight or  
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31 93 obese in Japan.[23][7] Recommended strategies for managing weight and obesity include

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34 94 lifestyle changes with appropriate dietary management and exercise. However, individuals with  
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37 95 an isolated  $BMI \geq 30 \text{ kg m}^{-2}$  or a  $BMI > 27 \text{ kg m}^{-2}$  with co-morbidities such as type 2 diabetes,  
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39 96 cardiovascular diseases, and obstructive sleep apnea, should receive pharmacotherapy as

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42 97 well.[24][8] Among the available anti-obesity medicines, phentermine, diethylpropion and  
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45 98 orlistat are approved by the U.S. Food and Drug Administration, but sibutramine has been  
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47 99 withdrawn from the market.[25, 26][9, 10] Of these anti-obesity medicines, only mazindol has

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50 100 been approved for use in Japan.[27][11] However, several of these anti-obesity medicines are  
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52 101 among those that are frequently imported into Japan for personal use.[28][12] Safety profile.

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105 The online purchase of medicine through the Internet is a growing and convenient practice for  
106 many consumers. This practice has also become one of the most popular, easiest and safest  
107 routes for counterfeit medicine traders.[6, 30-32][4, 13-15] The availability of counterfeit  
108 erectile dysfunction (ED) medicines was reported in Japan by a limited number of case  
109 investigations.[33, 34] In addition, a joint investigation done by four pharmaceutical industries  
110 in Japan reported that approximately 60% of ED medicines available in the Internet are  
111 counterfeited.[34] However, the quality of anti-obesity and diet medicines available through the  
112 Internet was still unknown. Since, all types of therapeutic classes of medicines are counterfeited  
113 from essential medicines to lifestyle drugs, Because lifestyle medicines are frequently targeted  
114 by counterfeiters, an collaborative investigation between the Ministry of Health and Labour  
115 Welfare (MHLW), Japan; Kanazawa University, Kanazawa; and Doshisha Women's College,  
116 Kyoto, Japan was conducted to survey the quality of anti-obesity medicines that were purchased  
117 through online medicine sites. This investigation also provided an understanding of the process  
118 by which unapproved medicines are being imported for and used by consumers in Japan.

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14 122 **METHODS**15  
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22 125 ~~study survey~~ during August 2009.  
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27 127 **Selection of Internet sites and sample collection**28  
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32 129 ~~The~~ Japanese keywords personal import agent (個人輸入代行), diet (ダイエット), and33  
34 130 anti-obesity (肥満) medicines were used on the Japanese Google search engine35  
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37 131 (www.google.co.jp). From a list of more than 140,000 results, first 500 were further screened38  
39 132 out to find online pharmacies or suppliers or brokers —that offer anti-obesity medicines40  
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42 133 provided that they did not mention their physical address in their websites. Websites with43  
44 134 physical address and/or blogs and advertise-only sites were excluded in this step. In the second45  
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47 135 through fourth steps, Searches were ~~also~~ made on websites that advertise and sell counterfeit48  
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50 136 Cialis (シアルリス), Levitra (レビトラ) and Viagra (バイアグラ). From our experiences on51  
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9 138 ~~may also offer counterfeits of other varieties of medicines.[5, 35] The physical characteristics of~~  
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11 139 ~~original and counterfeit Cialis and Levitra were both identified earlier by the Ministry of Health,~~  
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14 140 ~~Japan, and information on websites that sell counterfeit Viagra was provided by Pfizer.[16] As~~  
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17 141 ~~such, in the second step, the Japanese key words personal import agent (‘個人輸入代行’),~~  
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19 142 ~~Cialis (‘シアリス’), ‘50mg’ and ‘100mg’ were used and first 100 results were~~  
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22 143 ~~further screened out from a list of more than 35,000. In the third step, key words personal~~  
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24 144 ~~import agent (‘個人輸入代行’), Levitra (‘レビトラ’), ‘50mg’ and ‘100mg’ were~~  
25  
26  
27 145 ~~used and again first 100 results were screened out from a list of around 60,000. The physical~~  
28  
29 146 ~~characteristics (e.g.: color of genuine and counterfeits, strength, packaging etc.) of original and~~  
30  
31  
32 147 ~~counterfeit Cialis and Levitra were both identified earlier by the Ministry of Health, Japan.[33]~~  
33  
34 148 ~~In the fourth step, samples were purchased from nine internet sites where counterfeit Viagra~~  
35  
36  
37 149 ~~(バイアグラ) was offered in the past. The information on these sites was provided by Pfizer.~~  
38  
39  
40 150 ~~Finally, based on the information available from our previous research, we searched~~  
41  
42 151 ~~homepages of ten domestic brokers and four of them were selected for sampling.~~  
43  
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47 153 After the exclusion of blogs and advertisement-only sites, 36 sites were chosen for the purchase  
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49  
50 154 of anti-obesity medicines. ~~Some of the criteria used in choosing the sites included the absence~~  
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53 155 ~~of a physical address and the presence of suspicious advertisements.~~ A list of  
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9 156 overweight/anti-obesity medicines was sought on each of the selected sites. ~~Priority rankings~~  
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11 ~~were made of the list of Available medicines in the lists were numbered consecutively~~ according  
12  
13  
14 158 to their vertical or horizontal placement on the web pages, ~~excluding foods and drinks items. We~~  
15  
16 159 ~~purchased one anti-obesity medicine that was listed first in one of the selected sites. In the~~  
17  
18  
19 160 ~~subsequent selected websites, we purchased another brand or product of anti-obesity medicines,~~  
20  
21  
22 161 ~~which was listed first. Samples of the anti-obesity medicines were purchased from selected sites~~  
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24 162 ~~according to the smallest priority number found for a medicine that had not been purchased~~  
25  
26  
27 163 ~~from a previous website.~~  
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30 164

31  
32 165 Information on the site's name, URL, compliance with Japanese rules of "Act on Specified  
33  
34 166 Commercial Transaction" (ASCT), e-mail address, the name of the product and other  
35  
36  
37 167 information such as the dosage, efficacy and side effects, recommendation on consultation with  
38  
39  
40 168 doctors or pharmacists or opportunities for consultation were recorded while examining the sites  
41  
42 169 from which at least one product was purchased. ~~ASCT is the policy guidelines of all kinds of~~  
43  
44 170 ~~business transaction to protect interests of the consumers in Japan. These guidelines cover~~  
45  
46  
47 171 ~~door-to-door sales, mail order sales, telemarketing etc. According to the ASCT all e-commerce~~  
48  
49  
50 172 ~~sites in Japan should mention their name, address(es), telephone numbers, prices of~~  
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53 173 ~~commodities, shipment procedure(s) etc.[36]~~  
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11 175 **Observational analysis**

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14 176 All of the samples were given distinct codes when the shipments were received. The name of  
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17 177 the product, dosage form, content information from the printed label, the manufacturers' name  
18  
19 178 and address, the country of origin, the manufacture and expiration dates, lot, registration and  
20  
21  
22 179 license numbers, presence of package insert and their languages, Japanese ~~manual~~,  
23  
24 180 information/notes, information from the shipping company, the sending country, the date of  
25  
26  
27 181 shipment and arrival, and customs declaration notations were recorded for each of the samples.  
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31  
32 183 **Chemical analysis**

33  
34 184 Pharmacopoeial procedures for the analysis of the samples (i.e.: orlistat, sibutramine,  
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37 185 rimonabant, benfluorex and lovastatin) were established and performed using high performance  
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39  
40 186 liquid chromatography (HPLC), which are described briefly below. However, analytical  
41  
42 187 methods and results of rhei rhubarb and herbal products (i.e.: pahyma hoelen, ophiopogonis  
43  
44  
45 188 tuber and dai dai hua) were excluded, since they will be reported elsewhere.  
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49 190 Preparation of the sample solutions

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52 191 Randomly selected capsules of orlistat and sibutramine samples were weighed accurately. After  
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9 192 each capsule was weighed, the contents were removed, and the empty capsule shells were  
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11 193 subsequently weighed. The difference between the weight of the whole capsule and the capsule  
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14 194 shell was assumed to be the weight of the contents. To prepare sample solutions of lovastatin,  
15  
16 benfluorex and rimonabant tablets, randomly chosen tablets were weighed accurately and  
17 195 subsequently crushed separately into powder. Approximately 80 ml of methanol was added to  
18  
19 196  
20  
21 197 the capsule's contents or tablet powder, and the mixture was sonicated for 30 min. After  
22  
23  
24 198 sonication, methanol was then added to a volume of 100 ml. The resulting solutions were  
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26  
27 199 filtered through a membrane filter (pore size: 0.45  $\mu\text{m}$ ) and used as the sample solutions.  
28

29  
30 200  
31  
32 201 ~~To prepare sample solutions of lovastatin, benfluorex and rimonabant tablets, randomly chosen~~  
33  
34 202 ~~tablets were weighed accurately and subsequently crushed separately into powder.~~  
35  
36  
37 203 ~~Approximately 80 ml of methanol was added to the powder, and the solutions were sonicated~~  
38  
39 204 ~~for 30 min. Methanol was added to each of the solutions to a volume of 100 ml. The resulting~~  
40  
41  
42 205 ~~solutions were filtered through membrane filters (pore size: 0.45  $\mu\text{m}$ ) and used as the sample~~  
43  
44  
45 206 ~~solutions.~~  
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50 208 Preparation of standard solutions

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52 209 Three consecutive strengths of standard solutions were prepared by dissolving 0.375 mg, 0.75  
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9 210 mg and 1.50 mg of orlistat; 0.050 mg, 0.100 mg and 0.200 mg of sibutramine; 0.100 mg, 0.200

10  
11 211 mg and 0.500 mg of lovastatin; 0.100 mg, 1.50 mg and 2.00 mg of benfluorex; 0.100 mg, 0.200

12  
13  
14 212 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.

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17 213

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19 214 Assay condition

20  
21 215 Ten microliters of each sample solution and standard solution was placed in vials and assayed

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23 216 using a photodiode array of 225 nm wavelength (200–400 nm range for spectra) with a stainless

24  
25  
26 217 steel column with a 4.6 mm internal diameter and 15 cm length packed with octadecylsilanized

27  
28 218 silica gel for liquid chromatography (5 µm particle diameter) used with Mightysil RP-18 GP

29  
30 219 150-4.6. The column temperature was maintained at 45°C. A mixture of methanol and phosphate

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32 220 buffer, pH 7.0 (17:3) was used as the mobile phase at a flow rate of 1.2 ml/min.

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39 222 **Authenticity investigation**

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41 223 A catalogue and a questionnaire for all the samples were created that included the information

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43 224 from the printed labels of the product packages. The printed information was also checked

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45 225 against the information on the manufacturers' websites. The questionnaires were sent to the

46  
47 226 appropriate manufacturers with a portion of the samples for verification of their authenticity.

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50 227 The regulatory authorities for medicine in the country of origin were also contacted to verify the

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9 228 legitimacy of the products and their approval for marketing. After considering the WHO  
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11 229 definition of counterfeit medicines, the gathered information was analyzed to determine the  
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14 230 authenticity of the individual samples and their manufacturers. ~~[7, 37][17, 18]~~

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### 18 19 232 **Statistical analysis**

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21 233 Because of the small size of the sample, descriptive statistical analysis was performed using  
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24 234 Microsoft Excel.

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## 28 29 236 **RESULTS**

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32 237 ~~A total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet~~  
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34 238 ~~sites. Some of these products were shipped in divided shipments and treated as distinct samples.~~

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37 239 ~~In the first step of the Internet search, Of the selected internet sites, 15 sites were selected that~~  
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39 240 ~~did not show a physical address. In the second through fourth steps, and six, two and nine of~~  
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42 241 ~~the web sites were selected that concurrently~~ advertised counterfeit Cialis, Levitra and Viagra,  
43  
44 242 ~~respectively. Two of the sites with fake Cialis and Viagra also did not show a physical address.~~

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47 243 ~~Four of the websites were hosted by domestic shipping companies selected in the fifth step. A~~  
48  
49 244 ~~total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet~~  
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51  
52 245 ~~sites (Table 1). On average, these sites offered 62 kinds of products (including diet foods and~~

drinks). Some of these products were shipped in divided shipments and treated as distinct samples. However, only one of such identical samples was analyzed for pharmacopoeial quality.

Table 1. Active Ingredient

Active Ingredient	Approval status in Japan	n(%)	Classification
Sibutramine hydrochloride	Not approved	42 (51.2)	Prescription medicine
Orlistat	Not approved	15 (18.3)	Prescription medicine Over the counter: 5*
Rimonabant	Not approved	2 (2.4)	Prescription medicine
Benfluorex	Not approved	2 (2.4)	Prescription medicine
Lovastatin**	Not approved	2 (2.4)	Prescription medicine
<i>Pachyma hoelen</i> (茯苓)	Approved	14 (17.1)	Over the counter
<i>Ophiopogonis tuber</i> (麦門冬)	Approved	3 (3.6)	Over the counter
<i>Rhei</i> Rhubarb (大黄)**	Approved	1 (1.2)	Over the counter
Dai dai hua (代代花)	Approved	1 (1.2)	Over the counter
<b>Total</b>		<b>82 (100.0)</b>	

\*: Alli (orlistat 60 mg), \*\*: available under diet (ダイエット) search/ not classified as anti-obesity medicines

### Information available on the web sites

Different levels of compliance with ASCT were observed throughout all (36) of the web sites.<sup>[36]</sup> For instance, all (100%) of them mentioned the selling price, shipping charges for the goods, and methods of payment. However, only 21 (58.3%) of them provided telephone numbers, and only 17 (47.2%) of them mentioned a physical address.

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9 259 Information for e-mail addresses and shipment procedures were presented on all of the selected  
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11 260 sites. However, only 21 (58.3%) of them encouraged consumers to consult with a physician or  
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14 261 pharmacist. Consultation services were available at two (5.5%) of the sites. Dosage and  
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16 262 administration, effects and efficacy, and side effects related to the products were explained in 18  
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18  
19 263 (50%), 23 (63.8%) and 17 (47.2%) of the sites, respectively, despite the prohibition on  
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22 264 advertisements for unapproved medicines.  
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#### 27 266 **Information provided with the samples**

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29 267 Upon examination of the printed materials, the languages of the package inserts were found to  
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31  
32 268 be in English for 14 (17.1%) of the samples, Chinese for 13 (15.9%), both Chinese and Korean  
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34 269 for 10 (12.2%), both English and Chinese for 4 (4.9%), Turkish for 2 (2.4%), both English and  
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36  
37 270 Thai for 1 (1.2%), and English, Chinese and Russian for 1 (1.2%) of the samples. However, 37  
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39 271 ~~(45.1% (37))~~ of the samples did not have any package inserts.  
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42 272  
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#### 47 274 **Shipment of the samples**

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50 275 Samples were sent by 29 different shipping companies. The majority (13 companies) shipped  
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53 276 from China, and the second largest group was from India (4 companies). Others were shipped  
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9 277 from the USA (3), Japan (2), Thailand (2), Switzerland (1), Hong Kong (1), Cambodia (1), the  
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11 278 Fiji Islands (1), and Puerto Rico (1). The customs declaration was 'health product/personal  
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14 279 health items' for 20 (24.4%) of the samples, 'supplement' for 13 (15.9%) of the samples,  
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17 280 'medicine' for 10 (12.2%) of the samples and the actual name of the product in 2 (2.4%) cases.  
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19 281 However, 12 (14.7%) of the samples were shipped with a declaration of general merchandise  
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21 282 and/or tea, 11 (13.4%) of them declared 'other' and 14 (17.1%) of them did not mention  
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23  
24 283 anything as the declaration. Interestingly, one representative from an importing agent of a diet  
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27 284 medicine clinic (Sabairato Yanhee MD and clinic, <http://www.gop23.com>) inquired over the  
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29 285 telephone regarding the purpose for our purchase of the medicine and asked if we had any  
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32 286 relationship with the MHLW, Japan; they did not sell their products to us.  
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### 288 **Sample characteristics**

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39 289 Of the 82 samples, ~~423~~ (512.24%) were advertised on the websites as containing sibutramine  
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42 290 hydrochloride and 15 (18.3%) were advertised as orlistat. Rimonabant, benfluorex, and  
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45 291 lovastatin were advertised to be in two (2.4%) of the samples. Rhei rhubarb was said to be in  
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48 292 one, and the remaining ~~187~~ (210.97%) samples were advertised to be herbal products (Table 1).  
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50 293 ~~All these products were advertised by their brand names. The results of the rhubarb and herbal~~  
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53 294 ~~products will be reported elsewhere.~~ Out of the 64 synthetic products, 58 samples from 19  
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9 295 different products were prescription medicines, however, none of which requested a prescription  
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11 296 for the purchase. Five brands of orlistat were over-the-counter medicines, and one sample,  
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14 297 Daidai hua, was marketed as a natural supplement. Interestingly, daidai hua ~~However, this~~  
15  
16 298 ~~product~~ was advertised as sibutramine by its agent, and the sample actually contained  
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18  
19 299 sibutramine as shown by chemical analysis. According to purported country of marketing  
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21 300 authorization holder, 25 sibutramine products originated from India (dispatched from India,  
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23 301 Hong Kong and Fiji Islands), seven from China (dispatched from China), seven from Germany  
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25 302 (dispatched from Hong Kong and Cambodia) and three from Hong Kong (dispatched from  
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27 303 Cambodia). Among 15 orlistat products, seven originated from India (dispatched from India and  
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29 304 Japan), five from United Kingdom (dispatched from Switzerland, USA and Japan), two from  
30  
31 305 Switzerland (dispatched from Puerto Rico) and one from Thailand (dispatched from Thailand).  
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33 306 Two rimonabant, benfluorex and one lovastatin samples originated from India (dispatched from  
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35 307 Thailand and Japan), France (dispatched from Hong Kong) and USA (dispatched from USA)  
36  
37 308 respectively. All herbal products (including daidai hua) originated from China, except two (i.e.:  
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39 309 Pachyma hoelen), which are from USA, however, dispatched from China.  
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52 312 **Quality analysis**



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9 313 Out of total, 52 samples (i.e.: Sibutramine: 21, Orlistat: 13, Rimonabant: 2, Benfluorex: 2,  
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11 314 Lovastatin: 1 and herbal products: 13) were analyzed by HPLC to measure quantity of active  
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13  
14 315 ingredients in the samples. Thirty samples (received in divided shipments and identical with an  
15  
16 316 analyzed sample from a same source respectively) were excluded because of the insufficient  
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19 317 materials. Quantitative analysis by HPLC showed that all (21) of the samples of sibutramine  
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22 318 were in the acceptable range (90%-110%) except one (mean content percentage of 60.2±7.6).  
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24 319 No active ingredient was detected in three out of the 13 samples of orlistat that we tested  
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27 320 (Figure 1). These three samples were identified to be counterfeit. Of these three counterfeit  
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29 321 samples, two were found to be Xenical after analysis by the researchers and the manufacturer of  
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31 322 the genuine products. No active ingredient was detected in the last sample, only starch (Figure  
32  
33 323 1). The other counterfeit sample contained unknown excipients. None of the samples of  
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35 324 lovastatin, benfluorex or rimonabant failed the HPLC analysis.  
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#### 42 326 **Authenticity investigation**

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45 327 Responses to our requests for authentication were received from only five of the 20  
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47 328 manufacturing companies of the genuine samples. According to the responses that we received,  
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50 329 all of the responding manufacturers were GMP compliant. Of the 12 reported samples, two of  
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52 330 the orlistat samples (Xenical) from the same manufacturer were confirmed to be counterfeit  
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331 (Table 24).

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335 Table 24. Results of Authenticity Investigation

Active ingredient	<del>Labeled c</del> Country of <del>Authorized m</del> Marketing <del>authorization holder</del>	Genuine sample	Counterfeit sample	Manufacturing License
Orlistat (60 mg)	USA	5	0	YES
Benfluorex (150 mg)	France	2	0	YES
Rimonabant (20 mg)	India	1	0	YES
Orlistat (120 mg)	Switzerland	1	2	YES
Rhei Rhubarb	China	1	0	YES
*Orlistat (120 mg)	India	0	1	Unknown

336 \* labeled manufacturer did not reply

337

338 The counterfeit samples were purchased at [www.kenkoclinic.com](http://www.kenkoclinic.com) and sent to us from Puerto

339 Rico. They bore the same manufacture and expiration dates (MFD: 02/2011 and EXP: 02/2011,

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9 340 Figure 2) on their blisters, which had not yet occurred at the time of our investigation. The  
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11 341 printed information on the blisters of the counterfeits was a different color with a similar but  
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14 342 slightly different logo (Figure 3).  
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19 344 Telephone communications were made to the manufacturer of Zenigal (orlistat 120 mg) in India,  
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21 345 which did not contain any of the active ingredients that had been claimed on the product labels.  
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24 346 However, the manufacturer did not respond after several communication attempts. This  
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27 347 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of  
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29 348 counterfeit medicines at the rapid alert system of the Western Pacific Region of the World  
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32 349 Health Organization.  
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37 351 Responses were received from the medical regulatory authorities of three countries (Germany,  
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39 352 Switzerland and USA) for five of the manufacturers. Their responses stated that only orlistat has  
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42 353 approval to be manufactured in Switzerland. Approval for the manufacture of sibutramine in  
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45 354 Germany was suspended in January 2010, and it was not approved for use in the USA.  
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## 49 50 356 **DISCUSSION**

### 51 52 357 **Provided information on the samples**

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9 358 According to the Pharmaceutical Affairs Law (PAL) in Japan, advertising of unapproved  
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11 359 medicines is prohibited, and Customs should seize any shipment of prescription medicines when  
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13 360 the amount exceeds more than a one-month dose or any non-prescription medicines that exceed  
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15 361 more than a two-month dose. However, at least some of the samples in this study that exceeded  
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17 362 the approved amount for shipment made it through the regulatory checks during  
18  
19 363 shipping.<sup>[38][19]</sup> Surprisingly, at least four of the shipping companies are conducting business  
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21 364 in Japan. Contact information was not provided on many of the sites (52.8%), which seemingly  
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23 365 contradicts ASCT.<sup>[36][20]</sup> According to our study, nearly fifty percent of the sites mentioned  
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25 366 dosage administration, effects or side-effects of the medicines, which are not permitted by the  
26  
27 367 ~~pharmaceutical affairs laws (PAL)~~ in Japan.<sup>[38][19]</sup> As found in many previous studies on  
28  
29 368 e-medicines, approximately 50% of the samples did not contain a package insert.<sup>[35,</sup>  
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31 369 <sup>39-42][21-25]</sup> Moreover, several of the weight-loss products may contain harmful or  
32  
33 370 contraindicated ingredients.<sup>[33, 39][16, 21]</sup> ~~Similar to the findings of a recent study, none of the~~  
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35 371 ~~websites of our study required a prescription to purchase medicines.~~<sup>[43, 44]</sup>  
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### 373 Approval status of the products

374 The majority of the study samples were sibutramine, which is a selective inhibitor of the central  
375 neuronal reuptake of serotonin and noradrenaline and reduces food intake and body

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9 376 weight,<sup>[45][26]</sup> However, after conclusion of the safety review of sibutramine, the European  
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11 377 Medicines Agency (EMA) has suspended its marketing authorization in the European Union  
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13 378 (EU),<sup>[46][27]</sup> A recently published study reported that generic Figurer (sibutramine 10 mg),  
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16 379 even though it has not been reviewed by the responsible government (USA, the exporting  
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18 380 nation), is freely circulating via the Internet, which is a serious concern for public  
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21 381 health,<sup>[35][22]</sup> According to the medicine regulations of Hong Kong, Figurer does not need  
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24 382 manufacturing authorization because the medicine is manufactured in a foreign country. The  
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27 383 authorization status of Ali (orlistat 60 mg) as a prescription medicine has been recommended to  
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29 384 transition to a non-prescription medicine in the EU,<sup>[47][28]</sup> In a questionnaire conducted by  
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32 385 community pharmacists in Great Britain, orlistat is suspected to be misused by consumers, as  
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34 386 stated in their responses,<sup>[48][29]</sup> Similarly, marketing authorization for Acomplia (rimonabant)  
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37 387 has also been withdrawn in the EU in January 2009 and safety profiles of other anti-obesity  
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39 388 agents are generating controversy in different parts of the world,<sup>[49-53][30-33]</sup> Even though all  
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42 389 the anti-obesity agents sampled in this survey are unapproved in Japan, it is possible that anyone  
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45 390 can procure these items without declaring the actual contents during shipping.  
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50 392 **Authenticity and quality of the samples**  
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52 393 As similarly shown in previous studies, we observed low rates of authenticity,<sup>[54][34]</sup>

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394 Responses from only five (25%) of the manufacturers for 14.6% of the samples were received.

395 The counterfeit samples identified in this survey were confirmed by the manufacturer of the

396 corresponding genuine products. Counterfeiting of anti-obesity medicines, particularly orlistat,

397 has been previously reported.<sup>[55, 56]</sup>~~[35, 36]~~ Based on the external characteristics of the

398 counterfeits, these products most often differ in their printed information, design, color, etc.

399 from those of the genuine drugs.<sup>[17, 57]</sup>~~[37, 38]~~ As shown in some other studies, the

400 counterfeits detected in this survey did not contain any active ingredients.<sup>[54, 58]</sup>~~[34, 39]~~ It is

401 not clear why the manufacture of Zenigal, which failed the content analysis, did not respond to

402 our authentication request. In such a case, it can be assumed that the manufacturer is already

403 aware of the distribution of low-quality products in the pharmaceutical market. Several reports

404 suggest that patients have sought medical treatment for life-threatening complications after the

405 consumption of fake or substandard medicines purchased online.<sup>[59]</sup>~~[49]~~ When products are

406 purchased through the Internet and the sites are not sufficiently regulated, customers are left to

407 accept the consequences.

408

409 ~~According to the PAI, a person violating pharmaceutical regulation may be sentenced to an~~

410 ~~imprisonment of up to 3 years or imposed a penalty of up to JPY 3 million or both.<sup>[60]</sup> In case~~

411 ~~of such violation by a company, the penalty may be increased to a maximum JPY 100~~

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9 412 million.[60] Nevertheless, PAL has only jurisdiction to regulate domestic traders and has no  
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12 413 hold on foreign online traders. Strengthening international collaboration along with  
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14 414 public-private partnership initiatives may facilitate stemming out illegal internet trading hosted  
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17 415 from outside national boundaries.[19, 61, 62]  
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22 417 One of the limitations of the study might be small sample size, which may restrict study  
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24 418 findings to Japan. The sampling scheme may also limit our findings from generalization to all  
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27 419 internet sites. However, the sampling scheme was purposefully designed to investigate  
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30 420 suspicious online medicine sites. Our study was not designed comprehensively to explore  
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32 421 information during shipment of medicinal products especially at Japanese custom check.  
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34 422 Further evaluation with a representative sample may provide more information on the extent of  
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37 423 the problem. Low response rate of authenticity investigation may also be considered as a  
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40 424 limiting factor. However, better communication and cooperation among authentic manufacturers  
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43 425 and medicine regulatory authorities may increase response rate and generate more information  
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46 426 to counteract against counterfeits.

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## 48 49 50 428 **CONCLUSIONS**

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52 429 It is evident from this study that counterfeit, unapproved and suspended anti-obesity medicines  
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9 430 are circulating via the Internet. Because of gaps and the insufficient monitoring system of  
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11 431 imports for personal use in the rapidly growing e-commerce environment, these medicines can  
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14 432 easily enter into the distribution channels for pharmaceuticals and may pose health hazards for  
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16 433 consumers. Time has come to address such gaps of cross-border pharmaceutical e-commerce  
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19 434 and regulate the same through international cooperation and public-private partnerships.  
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21 435 Obviously, first and foremost step should be at country levels to make necessary amendments of  
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23 436 existing regulation focusing online pharmaceutical transactions. Furthermore, there might be an  
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25 437 urgent need at international level to formulate common regulation and agreements focusing  
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27 438 issues of pharmaceutical e-commerce.  
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37 441 **Acknowledgements** We gratefully acknowledge the cooperation received from the staff of  
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39 442 MHLW. ~~Additionally, we thank Ms. Hitomi Tabata for her cooperation in this work.~~  
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44 444 **Funding** This study was supported by ~~Health and Labour Sciences~~ Research Grants from the  
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46 445 MHLW, Japan.  
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52 447 **Competing interests** The authors declare no conflict of interest.  
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14 450 **Authors' contribution** MHK, TT, YN, and KK participated in the conception and design of the  
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16 451 study; TT, YN and KK participated in sampling activities and analysis of the samples; MHK, TT,  
17  
18 452 YN, NY, HT and KK participated in data analysis and interpretation of results. MHK wrote the  
19  
20 453 first draft of the manuscript. All authors contributed in the critical review of the draft manuscript,  
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22 454 editing and finally approved its submitted version.  
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32 457 **Data sharing statement** No additional data available.  
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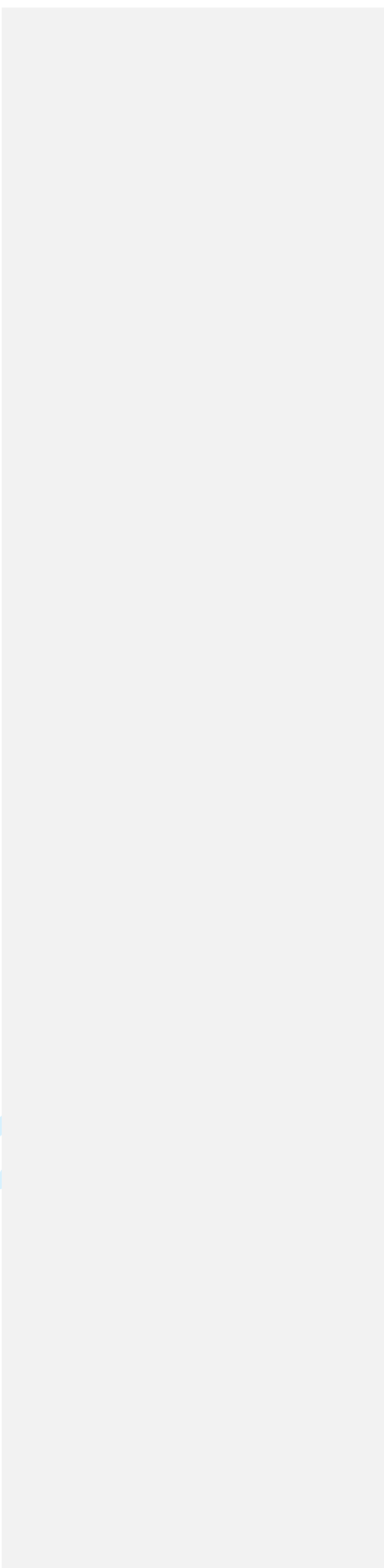
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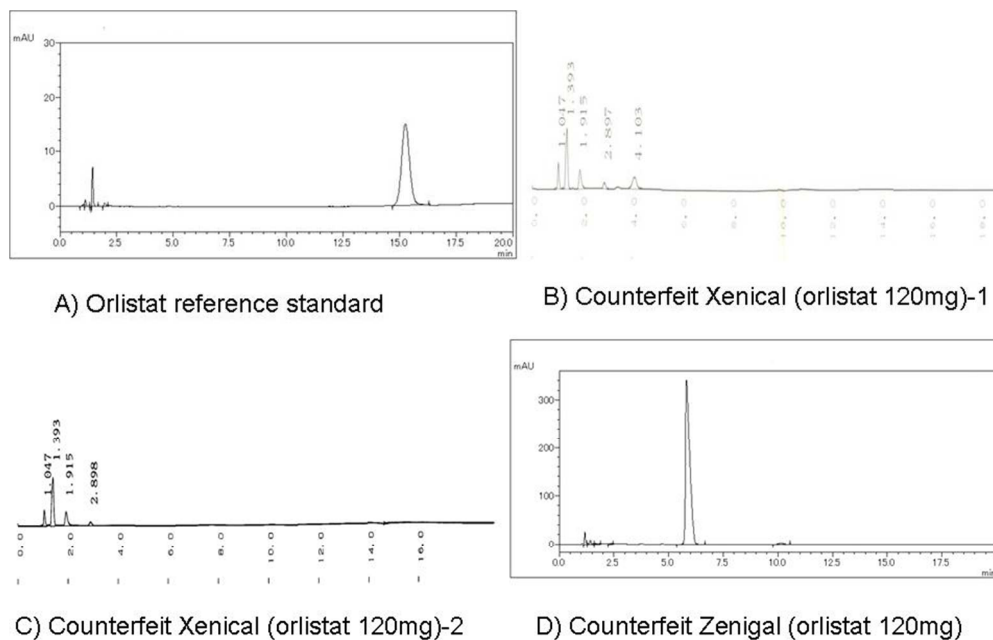


Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples  
254x190mm (96 x 96 DPI)

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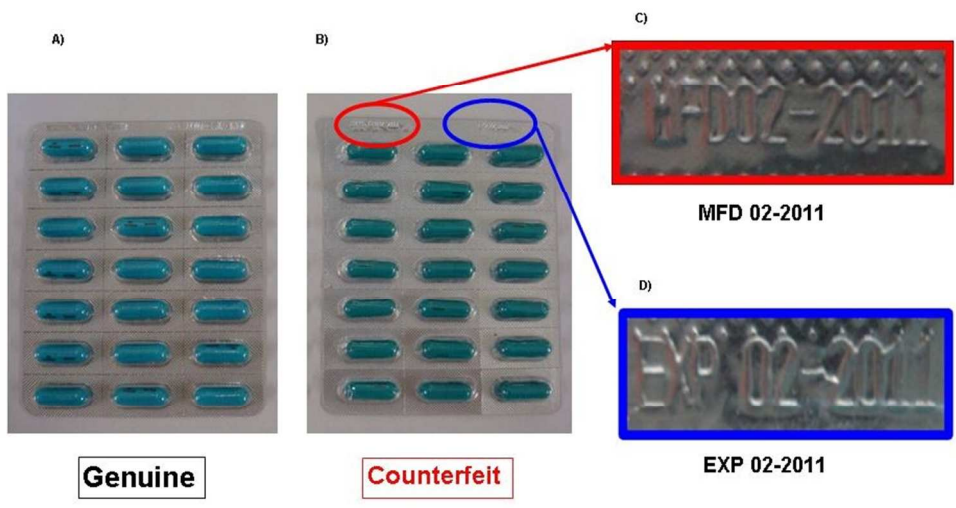


Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)  
254x190mm (96 x 96 DPI)

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Figure 3. Reverse side of blister: A) Logo of genuine sample, B) Logo of counterfeit sample  
254x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	N.A.
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	N.A.
		(c) Explain how missing data were addressed	N.A.
		(d) If applicable, describe analytical methods taking account of sampling strategy	N.A.
		(e) Describe any sensitivity analyses	N.A.
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13
		(b) Give reasons for non-participation at each stage	11-13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14
		(b) Indicate number of participants with missing data for each variable of interest	13-14
Outcome data	15*	Report numbers of outcome events or summary measures	14-16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N.A.
		(b) Report category boundaries when continuous variables were categorized	N.A.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	17-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).