



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

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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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14       medicine

15

## 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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34 an authenticity check even after several communication attempts. These counterfeit cases have  
35 been reported at the rapid alert system of Western Pacific Region of the World Health  
36 Organization.  
37 **Conclusion:** Many counterfeit and unapproved anti-obesity medicines may be easily bypassing  
38 regulatory checks during shipping and are widely circulated through the Internet. Regulatory  
39 authorities should take measures to prevent these medicines from entering countries to  
40 safeguard their citizens.

## ARTICLE SUMMARY

### Article Focus

- Quality of online anti-obesity medicines.
- Circulation of unapproved anti-obesity medicines via the Internet.

### Key Messages

- Counterfeit and substandard anti-obesity medicines, orlistat are identified.
- False and vague custom declarations were made by some of the shipping companies to by-pass regulatory checks of unapproved online medicines.

### Strength and Limitations

Small sample size and low authenticity response rate are limitations of this study.

However, the study provides valuable information for regulatory authorities on how unapproved and counterfeit medicines are being circulated through the Internet.

Concerted efforts of authentic manufacturers and medicine regulatory authorities are must to combat counterfeits and ensure access of quality medicines to online consumers.

63 INTRODUCTION

64 Over the past decade, the Internet has become an integral part of life for a variety of uses.  
65 Approximately 60% of Internet users in some developed countries utilize the Internet for their  
66 health related activities.[1, 2] In fact, when Internet users were asked about specific searches  
67 related to health, such as diet and fitness information or health insurance materials, 80% of the  
68 users in a 2002 survey said that they had performed these types of searches.[1] According to a  
69 survey taken in Japan, a majority (86.3%) of the medicines imported for personal use were  
70 purchased through the Internet.[3] However, according to World Health Organization, more than  
71 50% of the medicines from Internet sites, which often conceal their physical address, may be  
72 counterfeit or of substandard quality.[4]

73  
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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23  
24 87 into Japan for personal use.[12]  
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27 88  
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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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53 97 Japan.  
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99     **METHODS**

100    **Study design**

101    Quality of online anti-obesity medicines was assessed using an online cross-sectional survey  
102    during August 2009.

104    **Selection of Internet sites and sample collection**

105    The Japanese keywords personal import agent, diet, and anti-obesity medicines were used on  
106    the Japanese Google search engine ([www.google.co.jp](http://www.google.co.jp)) to find online pharmacies or suppliers  
107    that offer anti-obesity medicines. Searches were also made on websites that advertise and sell  
108    counterfeit Cialis, Levitra and Viagra. The physical characteristics of original and counterfeit  
109    Cialis and Levitra were both identified earlier by the Ministry of Health, Japan, and information  
110    on websites that sell counterfeit Viagra was provided by Pfizer.[16] After the exclusion of blogs  
111    and advertisement-only sites, 36 sites were chosen for the purchase of anti-obesity medicines.  
112    Some of the criteria used in choosing the sites included the absence of a physical address and  
113    the presence of suspicious advertisements. A list of overweight/anti-obesity medicines was  
114    sought on each of the selected sites. Priority rankings were made of the list of medicines  
115    according to their vertical or horizontal placement on the web pages. Samples of the anti-obesity  
116    medicines were purchased from selected sites according to the smallest priority number found



117 for a medicine that had not been purchased from a previous website.

118

119 Information on the site's name, URL, compliance with Japanese rules of "Act on Specified  
120 Commercial Transaction" (ASCT), e-mail address, the name of the product and other  
121 information such as the dosage, efficacy and side effects, recommendation on consultation with  
122 doctors or pharmacists or opportunities for consultation were recorded while examining the sites  
123 from which at least one product was purchased.

124

#### 125 **Observational analysis**

126 All of the samples were given distinct codes when the shipments were received. The name of  
127 the product, dosage form, content information from the printed label, the manufacturers' name  
128 and address, the country of origin, the manufacture and expiration dates, lot, registration and  
129 license numbers, Japanese manual, information from the shipping company, the sending country,  
130 the date of shipment and arrival, and customs declaration notations were recorded for each of  
131 the samples.

132

#### 133 **Chemical analysis**

134 Pharmacopoeial procedures for the analysis of the samples were established and performed

135 using high performance liquid chromatography (HPLC), which are described briefly below.

136

137 Preparation of the sample solutions

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

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

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

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

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

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

144 membrane filter (pore size: 0.45  $\mu$ m) and used as the sample solutions.

145

146 To prepare sample solutions of lovastatin, benfluorex and rimonabant tablets, randomly chosen

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

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

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

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

151 solutions.

152

153 Preparation of standard solutions

154 Three consecutive strengths of standard solutions were prepared by dissolving 0.375 mg, 0.75  
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  
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  
157 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.

158

159 Assay condition

160 Ten microliters of each sample solution and standard solution was placed in vials and assayed  
161 using a photodiode array of 225 nm wavelength (200–400 nm range for spectra) with a stainless  
162 steel column with a 4.6 mm internal diameter and 15 cm length packed with octadecylsilanized  
163 silica gel for liquid chromatography (5 µm particle diameter) used with Mightysil RP-18 GP  
164 150-4.6. The column temperature was maintained at 45°C. A mixture of methanol and phosphate  
165 buffer, pH 7.0 (17:3) was used as the mobile phase at a flow rate of 1.2 ml/min.

166

167 **Authenticity investigation**

168 A catalogue and a questionnaire for all the samples were created that included the information  
169 from the printed labels of the product packages. The printed information was also checked  
170 against the information on the manufacturers' websites. The questionnaires were sent to the

171 appropriate manufacturers with a portion of the samples for verification of their authenticity.  
172 The regulatory authorities for medicine in the country of origin were also contacted to verify the  
173 legitimacy of the products and their approval for marketing. After considering the WHO  
174 definition of counterfeit medicines, the gathered information was analyzed to determine the  
175 authenticity of the individual samples and their manufacturers.[17, 18]

176

177 **Statistical analysis**

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

180

181 **RESULTS**

182 A total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet  
183 sites. Some of these products were shipped in divided shipments and treated as distinct samples.  
184 Of the selected internet sites, 15 sites did not show a physical address, and six, two and nine of  
185 the web sites advertised counterfeit Cialis, Levitra and Viagra, respectively. Two of the sites  
186 with fake Cialis and Viagra also did not show a physical address. Four of the websites were  
187 hosted by domestic shipping companies.

188

189 **Information available on the web sites**

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

194

195 Information for e-mail addresses and shipment procedures were presented on all of the selected  
196 sites. However, only 21 (58.3%) of them encouraged consumers to consult with a physician or  
197 pharmacist. Consultation services were available at two (5.5%) of the sites. Dosage and  
198 administration, effects and efficacy, and side effects related to the products were explained in 18  
199 (50%), 23 (63.8%) and 17 (47.2%) of the sites, respectively, despite the prohibition on  
200 advertisements for unapproved medicines.

201

202 **Information provided with the samples**

203 Upon examination of the printed materials, the languages of the package inserts were found to  
204 be in English for 17.1% of the samples, Chinese for 15.9%, both Chinese and Korean for 12.2%,  
205 both English and Chinese for 4.9%, Turkish for 2.4%, both English and Thai for 1.2%, and  
206 English, Chinese and Russian for 1.2% of the samples. However, 45.1% (37) of the samples did

207 not have any package inserts.

208

209 **Shipment of the samples**

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

222

223 **Sample characteristics**

224 Of the 82 samples, 43 (52.4%) were advertised on the websites as containing sibutramine

hydrochloride and 15 (18.3%) were advertised as orlistat. Rimonabant, benfluorex, and lovastatin were advertised to be in two (2.4%) of the samples. Rhei rhubarb was said to be in one, and the remaining 17 (20.7%) samples were advertised to be herbal products. The results of the rhubarb and herbal products will be reported elsewhere. Out of the 64 synthetic products, 58 samples from 19 different products were prescription medicines, five brands of orlistat were over-the-counter medicines, and one sample, Daidai hua, was marketed as a natural supplement. However, this product was advertised as sibutramine by its agent, and the sample actually contained sibutramine as shown by chemical analysis.

### Quality analysis

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

243

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	Genuine sample	Counterfeit sample	Manufacturing License
	Authorized Marketer			
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



252

253 The counterfeit samples were purchased at [www.kenkoclinic.com](http://www.kenkoclinic.com) and sent to us from Puerto  
254 Rico. They bore the same manufacture and expiration dates (MFD: 02/2011 and EXP: 02/2011,  
255 Figure 2) on their blisters, which had not yet occurred at the time of our investigation. The  
256 printed information on the blisters of the counterfeits was a different color with a similar but  
257 slightly different logo (Figure 3).

258

259 Telephone communications were made to the manufacturer of Zenigal (orlistat 120 mg) in India,  
260 which did not contain any of the active ingredients that had been claimed on the product labels.  
261 However, the manufacturer did not respond after several communication attempts. This  
262 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of  
263 counterfeit medicines at the rapid alert system of the Western Pacific Region of the World  
264 Health Organization.

265

266 Responses were received from the medical regulatory authorities of three countries (Germany,  
267 Switzerland and USA) for five of the manufacturers. Their responses stated that only orlistat has  
268 approval to be manufactured in Switzerland. Approval for the manufacture of sibutramine in  
269 Germany was suspended in January 2010, and it was not approved for use in the USA.

270 **DISCUSSION**

271 **Provided information on the samples**

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

284

285 **Approval status of the products**

286 The majority of the study samples were sibutramine, which is a selective inhibitor of the central  
287 neuronal reuptake of serotonin and noradrenaline and reduces food intake and body weight.[26]

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

302

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

304 As similarly shown in previous studies, we observed low rates of authenticity.[34] Responses  
305 from only five (25%) of the manufacturers for 14.6% of the samples were received. The

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

318

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

324 generate more information to counteract against counterfeits.

325

## 326 CONCLUSIONS

327 It is evident from this study that counterfeit, unapproved and suspended anti-obesity medicines  
328 are circulating via the Internet. Because of gaps and the insufficient monitoring system of  
329 imports for personal use in the rapidly growing e-commerce environment, these medicines can  
330 easily enter into the distribution channels for pharmaceuticals and may pose health hazards for  
331 consumers.

332

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335

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338

339 **Competing interests** The authors declare no conflict of interest.

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342 **Authors' contribution** MHK, TT, YN, and KK participated in the conception and design of the  
343 study; TT, YN and KK participated in sampling activities and analysis of the samples; MHK, TT,  
344 YN, NY, HT and KK participated in data analysis and interpretation of results. MHK wrote the  
345 first draft of the manuscript. All authors contributed in the critical review of the draft manuscript,  
346 editing and finally approved its submitted version.

347

348 **Data sharing statement** No additional data available.

349

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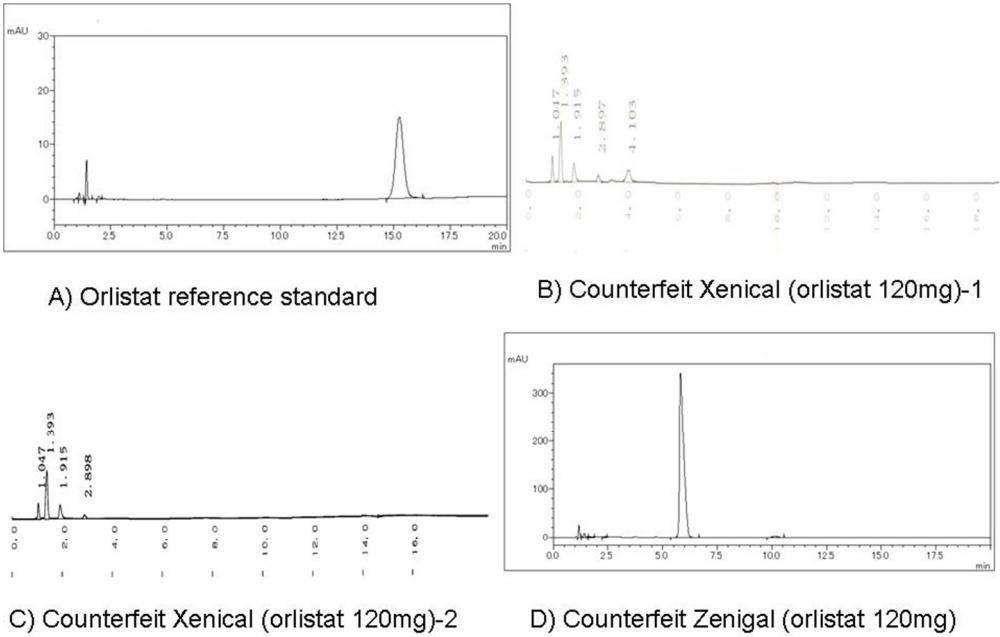
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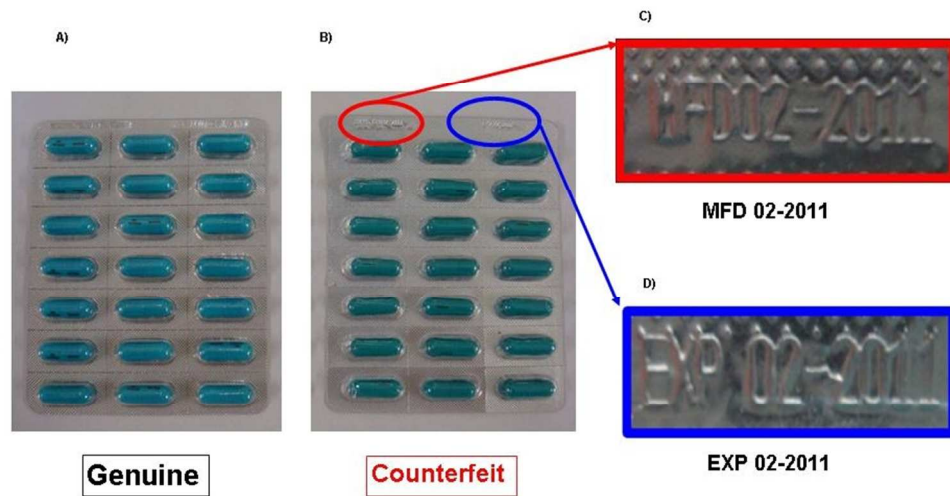


Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)  
254x190mm (96 x 96 DPI)



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
Introduction			
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
Methods			
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.
Results			

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
Discussion			
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
Other information			
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**

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

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

**Word counts:** 3,996088

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

## ABSTRACT

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

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

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

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

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

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

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35 | did not contain any active ingredients. ~~according to the chemical analyses.~~ Two of these  
36 | samples were confirmed as counterfeits by the manufacturer of the authentic products. The  
37 | manufacturer of the other sample did not respond to our request for an authenticity check even  
38 | after several communication attempts. These counterfeit cases have been reported at the rapid  
39 | alert system of Western Pacific Region of the World Health Organization.  
40 | **Conclusion:** Many counterfeit and unapproved anti-obesity medicines may be easily bypassing  
41 | regulatory checks during shipping and are widely circulated through the Internet. Regulatory  
42 | authorities should take measures to prevent these medicines from entering countries to  
43 | safeguard their citizens.

## ARTICLE SUMMARY

### Article Focus

- Quality of online anti-obesity medicines.
- Circulation of unapproved anti-obesity medicines via the Internet.

### Key Messages

- Counterfeit and substandard anti-obesity medicines, orlistat are identified.
- False and vague custom declarations were made by some of the shipping companies to by-pass regulatory checks of unapproved online medicines.

### Strengths and Limitations

Small sample size and low authenticity response rate are limitations of this study. However, the study provides valuable information for regulatory authorities on how unapproved and counterfeit medicines are being circulated through the Internet. Concerted efforts of authentic manufacturers and medicine regulatory authorities are a must to combat counterfeits and ensure access of quality medicines to online consumers.

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INTRODUCTION

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

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

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Obesity is becoming a major public health epidemic in this century and is associated with an increased risk for a number of health problems, such as hypertension, dyslipidemia, type 2 diabetes, and cardiovascular diseases.[21][5] The prevalence of obesity and its associated conditions are increasingly affecting both developed and developing countries over the last few decades.[22][6] Studies suggest that primarily adolescent and adult males are overweight or obese in Japan.[23][7] Recommended strategies for managing weight and obesity include lifestyle changes with appropriate dietary management and exercise. However, individuals with 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, cardiovascular diseases, and obstructive sleep apnea, should receive pharmacotherapy as well.[24][8] Among the available anti-obesity medicines, phentermine, diethylpropion and orlistat are approved by the U.S. Food and Drug Administration, but sibutramine has been withdrawn from the market.[25, 26][9, 10] Of these anti-obesity medicines, only mazindol has been approved for use in Japan.[27][11] However, several of these anti-obesity medicines are among those that are frequently imported into Japan for personal use.[28][12] Safety profile.

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risk vs benefit, cost-effectiveness of the investment deters manufacturers and marketers to get  
interested in approving anti-obesity medicines for Japanese market.[29]

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

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## METHODS

### Study design

Quality of online anti-obesity medicines was assessed using an online cross-sectional ~~study survey~~ during August 2009.

### Selection of Internet sites and sample collection

~~Internet sites were selected in five steps to purchase anti-obesity medicines. In the first step, the Japanese keywords personal import agent (個人輸入代行), diet (ダイエット), and anti-obesity (肥満) medicines were used on the Japanese Google search engine (www.google.co.jp). From a list of more than 140,000 results, first 500 were further screened out to find online pharmacies or suppliers or brokers—that offer anti-obesity medicines provided that they did not mention their physical address in their websites. That means sites with physical address and/or blogs and advertise-only sites were excluded in this step. In the second through fourth steps, Searches were also made on websites that advertise and sell counterfeit Cialis (シアリス), Levitra (レビトラ) and Viagra (バイアグラ). The physical characteristics of original and counterfeit Cialis and Levitra were both identified earlier by the~~

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~~Ministry of Health, Japan, and information on websites that sell counterfeit Viagra was provided~~  
~~by Pfizer.[16] As such, in the second step, the Japanese key words personal import agent (‘個人~~  
~~輸入代行’), Cialis (‘シアリス’), ‘50mg’ and ‘100mg’ were used and first 100~~  
~~results were further screened out from a list of more than 35,000 results to find out~~  
~~availability of anti-obesity medicines offered along side ED medicines. In the third step, key~~  
~~words personal import agent (‘個人輸入代行’), Levitra (‘レビトラ’), ‘50mg’ and~~  
~~‘100mg’ were used and again first 100 results were screened out from a list of around~~  
~~60,000 results. The physical characteristics (e.g.: color of genuine and counterfeits, strength,~~  
~~packaging etc.) of original and counterfeit Cialis and Levitra were both identified earlier by the~~  
~~Ministry of Health, Japan.[33] In the fourth step, samples were purchased from nine internet~~  
~~sites where counterfeit Viagra (バイアグラ) was offered in the past and information on these~~  
~~sites was provided by Pfizer. Finally, based on the information available from our previous~~  
~~research, we searched homepages of ten domestic brokers and four of them were selected~~  
~~for sampling.~~

After the exclusion of blogs and advertisement-only sites, 36 sites were chosen in total for the  
purchase of anti-obesity medicines. ~~Some of the criteria used in choosing the sites included the~~  
~~absence of a physical address and the presence of suspicious advertisements.~~ A list of

overweight/anti-obesity medicines was sought on each of the selected sites. ~~Priority rankings~~  
~~were made of the list of Available medicines in the lists were numbered consecutively~~ according  
to their vertical or horizontal placement on the web pages, ~~excluding foods and drinks items.~~  
Samples of the anti-obesity medicines were purchased from selected sites according to the  
smallest ~~priority~~ number found for a medicine that had not been purchased from a previous  
website.  
Information on the site's name, URL, compliance with Japanese rules of "Act on Specified  
Commercial Transaction" (ASCT), e-mail address, the name of the product and other  
information such as the dosage, efficacy and side effects, recommendation on consultation with  
doctors or pharmacists or opportunities for consultation were recorded while examining the sites  
from which at least one product was purchased. ~~ASCT is the policy guidelines of all kinds of  
business transaction in Japan to protect the interests of consumers. These guidelines cover  
door-to-door sales, mail order sales, telemarketing etc. According to the ASCT all e-commerce  
sites in Japan should mention their name, address(es), telephone numbers of the  
suppliers/brokers, prices of offered for commodities, shipment procedure(s) etc. in their  
advertisements.[35]~~

**Observational analysis**

All of the samples were given distinct codes when the shipments were received. The name of the product, dosage form, content information from the printed label, the manufacturers' name and address, the country of origin, the manufacture and expiration dates, lot, registration and license numbers, presence of package insert and their languages, Japanese ~~manual~~, information/notes, information from the shipping company, the sending country, the date of shipment and arrival, and customs declaration notations were recorded for each of the samples.

**Chemical analysis**

Pharmacopoeial procedures for the analysis of the samples (i.e.: orlistat, sibutramine, rimonabant, benfluorex and lovastatin) were established and performed using high performance liquid chromatography (HPLC), which are described briefly below. However, analytical methods and results of rhei rhubarb and herbal products (i.e.: pahyma hoelen, ophiopogonis tuber and dai dai hua) were excluded, since they will be reported elsewhere.

**Preparation of the sample solutions**

Randomly selected capsules of orlistat and sibutramine samples were weighed accurately. After 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  
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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  
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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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200 ~~To prepare sample solutions of lovastatin, benfluorex and rimonabant tablets, randomly chosen~~  
201 ~~tablets were weighed accurately and subsequently crushed separately into powder.~~  
202 ~~Approximately 80 ml of methanol was added to the powder, and the solutions were sonicated~~  
203 ~~for 30 min. Methanol was added to each of the solutions to a volume of 100 ml. The resulting~~  
204 ~~solutions were filtered through membrane filters (pore size: 0.45  $\mu\text{m}$ ) and used as the sample~~  
205 ~~solutions.~~  
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207 Preparation of standard solutions

208 Three consecutive strengths of standard solutions were prepared by dissolving 0.375 mg, 0.75  
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  
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11 211 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  
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23 216 steel column with a 4.6 mm internal diameter and 15 cm length packed with octadecylsilanized  
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25 217 silica gel for liquid chromatography (5 µm particle diameter) used with Mightysil RP-18 GP  
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27 218 150-4.6. The column temperature was maintained at 45°C. A mixture of methanol and phosphate  
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29 219 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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37 221 **Authenticity investigation**  
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39 222 A catalogue and a questionnaire for all the samples were created that included the information  
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41 223 from the printed labels of the product packages. The printed information was also checked  
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43 224 against the information on the manufacturers' websites. The questionnaires were sent to the  
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45 225 appropriate manufacturers with a portion of the samples for verification of their authenticity.  
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48 226 The regulatory authorities for medicine in the country of origin were also contacted to verify the  
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51 227 legitimacy of the products and their approval for marketing. After considering the WHO  
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definition of counterfeit medicines, the gathered information was analyzed to determine the authenticity of the individual samples and their manufacturers.<sup>[7, 36][17, 18]</sup>

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## Statistical analysis

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

## RESULTS

A total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet 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. Of the selected internet sites, 15 sites did not show a physical address, and six, two and nine of the web sites advertised counterfeit Cialis, Levitra and Viagra, respectively. Two of the sites with fake Cialis and Viagra also did not show a physical address. Four of the websites were hosted by domestic shipping companies.

Table 1. Active Ingredient

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

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<u>Orlistat</u>	<u>Not approved</u>	<u>15 (18.3)</u>	<u>Prescription medicine</u> <sup>10</sup>
			<u>Over the counter</u> : 5*
<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>	

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

Information available on the web sites

Different levels of compliance with ASCT were observed throughout all (36) of the web sites.<sup>[35]</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.

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

advertisements for unapproved medicines.

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#### Information provided with the samples

Upon examination of the printed materials, the languages of the package inserts were found to be in English for 14 (17.1%) of the samples, Chinese for 13 (15.9%), both Chinese and Korean for 10 (12.2%), both English and Chinese for 4 (4.9%), Turkish for 2 (2.4%), both English and Thai for 1 (1.2%), and English, Chinese and Russian for 1 (1.2%) of the samples. However, 37 (45.1%~~-(37)~~) of the samples did not have any package inserts.

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#### Shipment of the samples

Samples were sent by 29 different shipping companies. The majority (13 companies) shipped from China, and the second largest group was from India (4 companies). Others were shipped from the USA (3), Japan (2), Thailand (2), Switzerland (1), Hong Kong (1), Cambodia (1), the Fiji Islands (1), and Puerto Rico (1). The customs declaration was 'health product/personal health items' for 20 (24.4%) of the samples, 'supplement' for 13 (15.9%) of the samples, 'medicine' for 10 (12.2%) of the samples and the actual name of the product in 2 (2.4%) cases. However, 12 (14.7%) of the samples were shipped with a declaration of general merchandise and/or tea, 11 (13.4%) of them declared 'other' and 14 (17.1%) of them did not mention

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

**Sample characteristics**

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

Hong Kong and Fiji Islands), seven from China (dispatched from China), seven from Germany  
(dispatched from Hong Kong and Cambodia) and three from Hong Kong (dispatched from  
Cambodia). Among 15 orlistat products, seven originated from India (dispatched from India and  
Japan), five from United Kingdom (dispatched from Switzerland, USA and Japan), two from  
Switzerland (dispatched from Puerto Rico) and one from Thailand (dispatched from Thailand).  
Two rimonabant, benfluorex and one lovastatin samples originated from India (dispatched from  
Thailand and Japan), France (dispatched from Hong Kong) and USA (dispatched from USA)  
respectively. All herbal products (including daidai hua) originated from China, except two (i.e.:  
*Pachyma hoelen*), which are from USA, however, dispatched from China.

#### **Quality analysis**

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

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

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found to be Xenical after analysis by the researchers and the manufacturer of the genuine products. No active ingredient was detected in the last sample, only starch (Figure 1). The other counterfeit sample contained unknown excipients. None of the samples of lovastatin, benfluorex or rimonabant failed the HPLC analysis.

**Authenticity investigation**

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

Table 24. Results of Authenticity Investigation

	<del>Labeled c</del> Country of	Genuine	Counterfeit	Manufacturing
Active ingredient	<del>Authorized-m</del> Marketing	sample	sample	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

\* labeled manufacturer did not reply

The counterfeit samples were purchased at [www.kenkoclinic.com](http://www.kenkoclinic.com) and sent to us from Puerto Rico. They bore the same manufacture and expiration dates (MFD: 02/2011 and EXP: 02/2011, Figure 2) on their blisters, which had not yet occurred at the time of our investigation. The printed information on the blisters of the counterfeits was a different color with a similar but slightly different logo (Figure 3).

Telephone communications were made to the manufacturer of Zenigal (orlistat 120 mg) in India, which did not contain any of the active ingredients that had been claimed on the product labels. However, the manufacturer did not respond after several communication attempts. This

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340 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of  
341 counterfeit medicines at the rapid alert system of the Western Pacific Region of the World  
342 Health Organization.  
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344 Responses were received from the medical regulatory authorities of three countries (Germany,  
345 Switzerland and USA) for five of the manufacturers. Their responses stated that only orlistat has  
346 approval to be manufactured in Switzerland. Approval for the manufacture of sibutramine in  
347 Germany was suspended in January 2010, and it was not approved for use in the USA.

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349 **DISCUSSION**

350 **Provided information on the samples**

351 According to the Pharmaceutical Affairs Law in Japan, advertising of unapproved medicines is  
352 prohibited, and Customs should seize any shipment of prescription medicines when the amount  
353 exceeds more than a one-month dose or any non-prescription medicines that exceed more than a  
354 two-month dose. However, at least some of the samples in this study that exceeded the approved  
355 amount for shipment made it through the regulatory checks during shipping.<sup>[37][19]</sup>  
356 Surprisingly, at least four of the shipping companies are conducting business in Japan. Contact  
357 information was not provided on many of the sites (52.8%), which seemingly contradicts



358 ASCT.<sup>[35][20]</sup> According to our study, nearly fifty percent of the sites mentioned dosage

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359 administration, effects or side-effects of the medicines, which are not permitted by the

360 pharmaceutical affairs laws (PAL) in Japan.<sup>[37][49]</sup> As found in many previous studies on

361 e-medicines, approximately 50% of the samples did not contain a package insert.<sup>[38-42][21-25]</sup>

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362 Moreover, several of the weight-loss products may contain harmful or contraindicated

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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364 study required a prescription to purchase medicines.<sup>[43, 44]</sup>

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## 366 Approval status of the products

367 The majority of the study samples were sibutramine, which is a selective inhibitor of the central

368 neuronal reuptake of serotonin and noradrenaline and reduces food intake and body

369 weight.<sup>[45][26]</sup> However, after conclusion of the safety review of sibutramine, the European

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370 Medicines Agency (EMA) has suspended its marketing authorization in the European Union

371 (EU).<sup>[46][27]</sup> A recently published study reported that generic Figurer (sibutramine 10 mg),

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372 even though it has not been reviewed by the responsible government (USA, the exporting

373 nation), is freely circulating via the Internet, which is a serious concern for public

374 health.<sup>[39][22]</sup> According to the medicine regulations of Hong Kong, Figurer does not need

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375 manufacturing authorization because the medicine is manufactured in a foreign country. The

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authorization status of Alli (orlistat 60 mg) as a prescription medicine has been recommended to transition to a non-prescription medicine in the EU.<sup>[47][28]</sup> In a questionnaire conducted by community pharmacists in Great Britain, orlistat is suspected to be misused by consumers, as stated in their responses.<sup>[48][29]</sup> Similarly, marketing authorization for Acomplia (rimonabant) has also been withdrawn in the EU in January 2009 and safety profiles of other anti-obesity agents are generating controversy in different parts of the world.<sup>[49-53][30-33]</sup> Even though all the anti-obesity agents sampled in this survey are unapproved in Japan, it is possible that anyone can procure these items without declaring the actual contents during shipping.

**Authenticity and quality of the samples**

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

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

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

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

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internet sites. However, the sampling scheme was purposefully designed to investigate suspicious online medicine sites. Our study was not designed comprehensively to explore information during shipment of medicinal products especially at Japanese custom check.

Further evaluation with a representative sample may provide more information on the extent of the problem. Low response rate of authenticity investigation may also be considered as a limiting factor. However, better communication and cooperation among authentic manufacturers and medicine regulatory authorities may increase response rate and generate more information to counteract against counterfeits.

**CONCLUSIONS**

It is evident from this study that counterfeit, unapproved and suspended anti-obesity medicines are circulating via the Internet. Because of gaps and the insufficient monitoring system of imports for personal use in the rapidly growing e-commerce environment, these medicines can easily enter into the distribution channels for pharmaceuticals and may pose health hazards for consumers. Time has come to address such gaps of cross-border pharmaceutical e-commerce and to regulate through international cooperation and public-private partnerships. Obviously, first and foremost step should be at country levels to make necessary amendments of existing regulation focusing online pharmaceutical transactions. Side by side, there might be an urgent

need at international level to formulate common regulation and agreements focusing issues of pharmaceutical e-commerce.

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**Competing interests** The authors declare no conflict of interest.

**Authors' contribution** MHK, TT, YN, and KK participated in the conception and design of the study; TT, YN and KK participated in sampling activities and analysis of the samples; MHK, TT, YN, NY, HT and KK participated in data analysis and interpretation of results. MHK wrote the first draft of the manuscript. All authors contributed in the critical review of the draft manuscript, editing and finally approved its submitted version.

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449 **Data sharing statement** No additional data available.

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For peer review only

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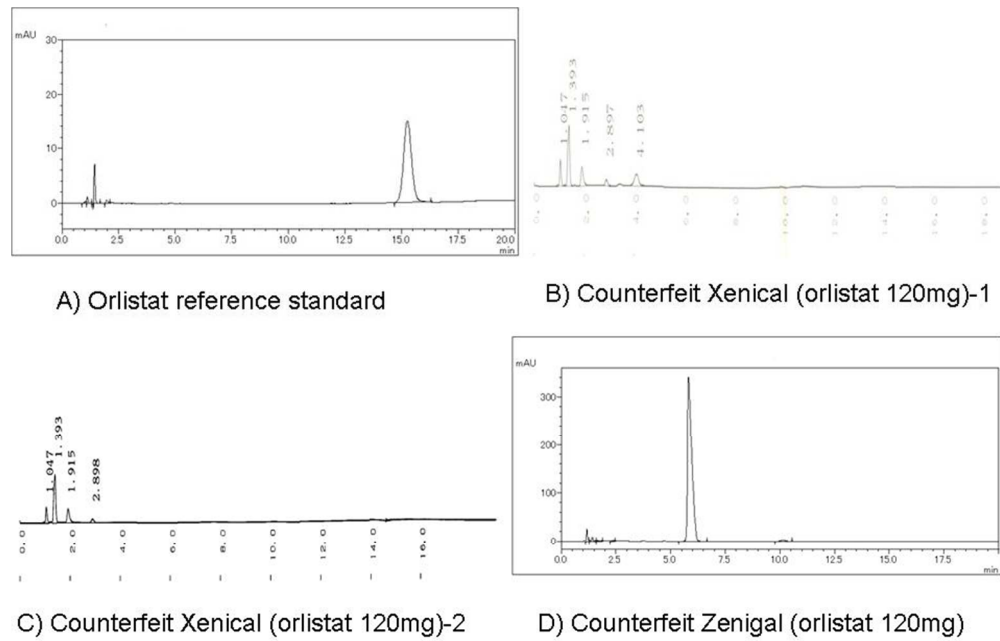


Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples  
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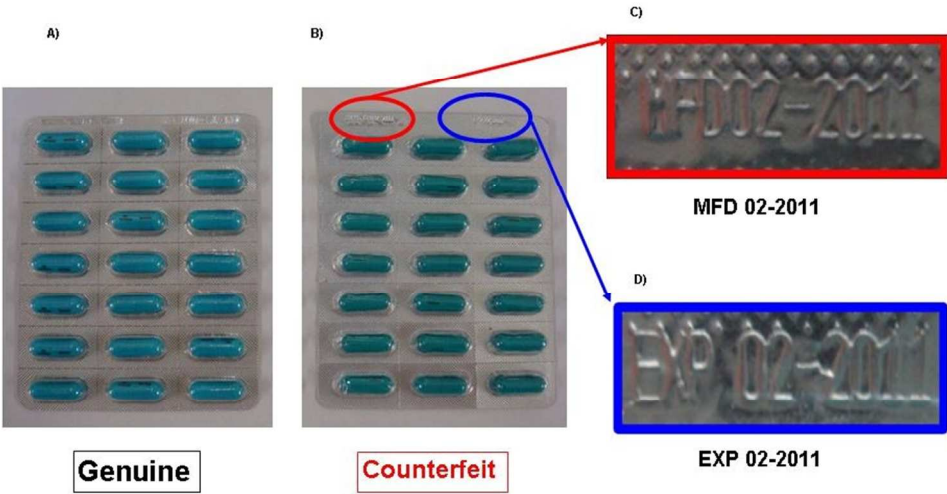


Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)  
254x190mm (96 x 96 DPI)



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
Introduction			
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
Methods			
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.
Results			

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**

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

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

**Word counts:** ~~3,399~~2088

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

## ABSTRACT

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

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

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

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

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

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



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35 | did not contain any active ingredients. ~~according to the chemical analyses.~~ Two of these  
36 | samples were confirmed as counterfeits by the manufacturer of the authentic products. The  
37 | manufacturer of the other sample did not respond to our request for an authenticity check even  
38 | after several communication attempts. These counterfeit cases have been reported at the rapid  
39 | alert system of Western Pacific Region of the World Health Organization.  
40 | **Conclusion:** Many counterfeit and unapproved anti-obesity medicines may be easily bypassing  
41 | regulatory checks during shipping and are widely circulated through the Internet. Regulatory  
42 | authorities should take measures to prevent these medicines from entering countries to  
43 | safeguard their citizens.

## ARTICLE SUMMARY

### Article Focus

- Quality of online anti-obesity medicines.
- Circulation of unapproved anti-obesity medicines via the Internet.

### Key Messages

- Counterfeit and substandard anti-obesity medicines, orlistat are identified.
- False and vague custom declarations were made by some of the shipping companies to by-pass regulatory checks of unapproved online medicines.

### Strengths and Limitations

Small sample size and low authenticity response rate are limitations of this study. However, the study provides valuable information for regulatory authorities on how unapproved and counterfeit medicines are being circulated through the Internet. Concerted efforts of authentic manufacturers and medicine regulatory authorities are a must to combat counterfeits and ensure access of quality medicines to online consumers.

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**INTRODUCTION**

Over the past decade, the Internet has become an integral part of life for a variety of uses. Approximately 60% of Internet users in some developed countries, such as Japan and United States of America (USA), utilize the Internet for their health related activities. ~~[1-4]~~~~[1, 2]~~ In fact, when Internet users were asked about specific searches related to health, such as diet and fitness information or health insurance materials, 80% of the users among adult Americans in a 2002 survey said that they had performed these types of searches.<sup>[1]</sup> According to a survey taken in Japan, a majority (86.3%) of the medicines imported for personal use were purchased through the Internet. ~~[5]~~~~[3]~~ However, according to World Health Organization (WHO), more than 50% of the medicines from Internet sites, which often conceal their physical address, may be counterfeit or of substandard quality. ~~[6]~~~~[4]~~

WHO defines counterfeit medicines as ones which are deliberately and fraudulently mislabeled with respect to identity and/or source.[7-9] On the other hand, substandard medicines are legitimate ones that do not meet the quality specifications claimed by their manufacturers.[10]

A number of reports documented the severity of drug counterfeiting during the last two decades. WHO found that 20-90% of drugs were counterfeited in some African countries.[11, 12] In Tanzania, 12.2% of antimalarials were identified as substandard in 2005.[13] In 2009, 37% of

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

Obesity is becoming a major public health epidemic in this century and is associated with an increased risk for a number of health problems, such as hypertension, dyslipidemia, type 2 diabetes, and cardiovascular diseases.[21][5] The prevalence of obesity and its associated conditions are increasingly affecting both developed and developing countries over the last few decades.[22][6] Studies suggest that primarily adolescent and adult males are overweight or obese in Japan.[23][7] Recommended strategies for managing weight and obesity include lifestyle changes with appropriate dietary management and exercise. However, individuals with 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, cardiovascular diseases, and obstructive sleep apnea, should receive pharmacotherapy as well.[24][8] Among the available anti-obesity medicines, phentermine, diethylpropion and orlistat are approved by the U.S. Food and Drug Administration, but sibutramine has been withdrawn from the market.[25, 26][9, 10] Of these anti-obesity medicines, only mazindol has been approved for use in Japan.[27][11] However, several of these anti-obesity medicines are among those that are frequently imported into Japan for personal use.[28][12] Safety profile.

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risk vs benefit, cost-effectiveness of investment deter manufacturers and marketers to get  
interested in approving anti-obesity medicines for Japanese market.[29]

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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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## 122 METHODS

### 123 Study design

124 Quality of online anti-obesity medicines was assessed using an online cross-sectional  
125 ~~study survey~~ during August 2009.

126

### 127 Selection of Internet sites and sample collection

128 Internet sites were selected in five steps to purchase anti-obesity medicines. In the first step,

129 ~~The~~ Japanese keywords personal import agent (個人輸入代行), diet (ダイエット), and

130 ~~anti-obesity (肥満) medicines~~ were used on the Japanese Google search engine

131 (www.google.co.jp). From a list of more than 140,000 results, first 500 were further screened

132 out to find online pharmacies or suppliers or brokers —that offer anti-obesity medicines

133 provided that they did not mention their physical address in their websites. Websites with

134 physical address and/or blogs and advertise-only sites were excluded in this step. In the second

135 through fourth steps, Searches were ~~also~~ made on websites that advertise and sell counterfeit

136 Cialis (シアリス), Levitra (レビトラ) and Viagra (バイアグラ). From our experiences on

137 previous online medicine studies, we presumed that the websites offer counterfeit ED drugs.

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~~may also offer counterfeits of other varieties of medicines.[5, 35] The physical characteristics of~~  
~~original and counterfeit Cialis and Levitra were both identified earlier by the Ministry of Health,~~  
~~Japan, and information on websites that sell counterfeit Viagra was provided by Pfizer.[16] As~~  
~~such, in the second step, the Japanese key words personal import agent (‘個人輸入代行’),~~  
~~Cialis (‘シアリス’), ‘50mg’ and ‘100mg’ were used and first 100 results were~~  
~~further screened out from a list of more than 35,000. In the third step, key words personal~~  
~~import agent (‘個人輸入代行’), Levitra (‘レビトラ’), ‘50mg’ and ‘100mg’ were~~  
~~used and again first 100 results were screened out from a list of around 60,000. The physical~~  
~~characteristics (e.g.: color of genuine and counterfeits, strength, packaging etc.) of original and~~  
~~counterfeit Cialis and Levitra were both identified earlier by the Ministry of Health, Japan.[33]~~  
~~In the fourth step, samples were purchased from nine internet sites where counterfeit Viagra~~  
~~(バイアグラ) was offered in the past. The information on these sites was provided by Pfizer.~~  
~~Finally, based on the information available from our previous research, we searched~~  
~~homepages of ten domestic brokers and four of them were selected for sampling.~~

After the exclusion of blogs and advertisement-only sites, 36 sites were chosen for the purchase  
of anti-obesity medicines. ~~Some of the criteria used in choosing the sites included the absence~~  
~~of a physical address and the presence of suspicious advertisements.~~ A list of

overweight/anti-obesity medicines was sought on each of the selected sites. ~~Priority rankings~~  
~~were made of the list of Available medicines in the lists were numbered consecutively~~ according  
to their vertical or horizontal placement on the web pages, ~~excluding foods and drinks items. We~~  
~~purchased one anti-obesity medicine that was listed first in one of the selected sites. In the~~  
~~subsequent selected websites, we purchased another brand or product of anti-obesity medicines,~~  
~~which was listed first~~ Samples of the anti-obesity medicines were purchased from selected sites  
~~according to the smallest priority number found for a medicine that had not been purchased~~  
~~from a previous website.~~

Information on the site's name, URL, compliance with Japanese rules of "Act on Specified  
Commercial Transaction" (ASCT), e-mail address, the name of the product and other  
information such as the dosage, efficacy and side effects, recommendation on consultation with  
doctors or pharmacists or opportunities for consultation were recorded while examining the sites  
from which at least one product was purchased. ~~ASCT is the policy guidelines of all kinds of~~  
~~business transaction to protect interests of the consumers in Japan. These guidelines cover~~  
~~door-to-door sales, mail order sales, telemarketing etc. According to the ASCT all e-commerce~~  
~~sites in Japan should mention their name, address(es), telephone numbers, prices of~~  
~~commodities, shipment procedure(s) etc.[36]~~



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175 **Observational analysis**

176 All of the samples were given distinct codes when the shipments were received. The name of

177 the product, dosage form, content information from the printed label, the manufacturers' name

178 and address, the country of origin, the manufacture and expiration dates, lot, registration and

179 license numbers, presence of package insert and their languages, Japanese—manual,

180 information/notes, information from the shipping company, the sending country, the date of

181 shipment and arrival, and customs declaration notations were recorded for each of the samples.

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183 **Chemical analysis**

184 Pharmacopoeial procedures for the analysis of the samples (i.e.: orlistat, sibutramine,

185 rimonabant, benfluorex and lovastatin) were established and performed using high performance

186 liquid chromatography (HPLC), which are described briefly below. However, analytical

187 methods and results of rhei rhubarb and herbal products (i.e.: pahyma hoelen, ophiopogonis

188 tuber and dai dai hua) were excluded, since they will be reported elsewhere.

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190 Preparation of the sample solutions

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

each capsule was weighed, the contents were removed, and the empty capsule shells were subsequently weighed. The difference between the weight of the whole capsule and the capsule shell was assumed to be the weight of the contents. To prepare sample solutions of lovastatin, benfluorex and rimonabant tablets, randomly chosen tablets were weighed accurately and subsequently crushed separately into powder. Approximately 80 ml of methanol was added to the capsule's contents or tablet powder, and the mixture was sonicated for 30 min. After sonication, methanol was then added to a volume of 100 ml. The resulting solutions were filtered through a membrane filter (pore size: 0.45 µm) and used as the sample solutions.

~~To prepare sample solutions of lovastatin, benfluorex and rimonabant tablets, randomly chosen tablets were weighed accurately and subsequently crushed separately into powder. Approximately 80 ml of methanol was added to the powder, and the solutions were sonicated for 30 min. Methanol was added to each of the solutions to a volume of 100 ml. The resulting solutions were filtered through membrane filters (pore size: 0.45 µm) and used as the sample solutions.~~

Preparation of standard solutions

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  
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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  
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14 212 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.  
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19 214 Assay condition  
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22 215 Ten microliters of each sample solution and standard solution was placed in vials and assayed  
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24 216 using a photodiode array of 225 nm wavelength (200–400 nm range for spectra) with a stainless  
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27 217 steel column with a 4.6 mm internal diameter and 15 cm length packed with octadecylsilanized  
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29 218 silica gel for liquid chromatography (5 µm particle diameter) used with Mightysil RP-18 GP  
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32 219 150–4.6. The column temperature was maintained at 45°C. A mixture of methanol and phosphate  
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34 220 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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42 223 A catalogue and a questionnaire for all the samples were created that included the information  
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44 224 from the printed labels of the product packages. The printed information was also checked  
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47 225 against the information on the manufacturers’ websites. The questionnaires were sent to the  
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50 226 appropriate manufacturers with a portion of the samples for verification of their authenticity.  
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53 227 The regulatory authorities for medicine in the country of origin were also contacted to verify the  
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legitimacy of the products and their approval for marketing. After considering the WHO definition of counterfeit medicines, the gathered information was analyzed to determine the authenticity of the individual samples and their manufacturers.<sup>[7, 37][17, 18]</sup>

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### Statistical analysis

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

## RESULTS

~~A total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet sites. Some of these products were shipped in divided shipments and treated as distinct samples. In the first step of the Internet search, Of the selected internet sites, 15 sites were selected that did not show a physical address. In the second through fourth steps, and six, two and nine of the web sites were selected that concurrently advertised counterfeit Cialis, Levitra and Viagra, respectively. Two of the sites with fake Cialis and Viagra also did not show a physical address. Four of the websites were hosted by domestic shipping companies selected in the fifth step. A total of 82 samples from 31 varieties of anti-obesity products were purchased from 36 internet 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
Rimonabant	Not approved	2 (2.4)	Prescription medicine
Benfluorex	Not approved	2 (2.4)	Prescription medicine
Lovastatin**	Not approved	2 (2.4)	Prescription medicine
Pachyma hoelen (茯苓)	Approved	14 (17.1)	Over the counter
Ophiopogonis tuber (麦門冬)	Approved	3 (3.6)	Over the counter
Rhei Rhubarb (大黄)**	Approved	1 (1.2)	Over the counter
Dai dai hua (代代花)	Approved	1 (1.2)	Over the counter
Total		82 (100.0)	

\*: 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.[36] 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.

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

#### Information provided with the samples

Upon examination of the printed materials, the languages of the package inserts were found to be in English for 14 (17.1%) of the samples, Chinese for 13 (15.9%), both Chinese and Korean for 10 (12.2%), both English and Chinese for 4 (4.9%), Turkish for 2 (2.4%), both English and Thai for 1 (1.2%), and English, Chinese and Russian for 1 (1.2%) of the samples. However, 37 (45.1%) of the samples did not have any package inserts.

#### Shipment of the samples

Samples were sent by 29 different shipping companies. The majority (13 companies) shipped from China, and the second largest group was from India (4 companies). Others were shipped

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277 from the USA (3), Japan (2), Thailand (2), Switzerland (1), Hong Kong (1), Cambodia (1), the  
278 Fiji Islands (1), and Puerto Rico (1). The customs declaration was ‘health product/personal  
279 health items’ for 20 (24.4%) of the samples, ‘supplement’ for 13 (15.9%) of the samples,  
280 ‘medicine’ for 10 (12.2%) of the samples and the actual name of the product in 2 (2.4%) cases.  
281 However, 12 (14.7%) of the samples were shipped with a declaration of general merchandise  
282 and/or tea, 11 (13.4%) of them declared ‘other’ and 14 (17.1%) of them did not mention  
283 anything as the declaration. Interestingly, one representative from an importing agent of a diet  
284 medicine clinic (Sabairato Yanhee MD and clinic, <http://www.gop23.com>) inquired over the  
285 telephone regarding the purpose for our purchase of the medicine and asked if we had any  
286 relationship with the MHLW, Japan; they did not sell their products to us.

287

288 **Sample characteristics**

289 Of the 82 samples, ~~423~~ (5~~12.24~~<sup>12.24</sup>%) were advertised on the websites as containing sibutramine  
290 hydrochloride and 15 (18.3%) were advertised as orlistat. Rimonabant, benfluorex, and  
291 lovastatin were advertised to be in two (2.4%) of the samples. Rhei rhubarb was said to be in  
292 one, and the remaining ~~187~~ (2~~10.97~~<sup>10.97</sup>%) samples were advertised to be herbal products ([Table 1](#)).  
293 ~~All these products were advertised by their brand names. The results of the rhubarb and herbal~~  
294 ~~products will be reported elsewhere.~~ Out of the 64 synthetic products, 58 samples from 19

different products were prescription medicines, however, none of which requested a prescription for the purchase. ~~Five~~ Five brands of orlistat were over-the-counter medicines, and one sample, Daidai hua, was marketed as a natural supplement. Interestingly, daidai hua ~~However, this product~~ was advertised as sibutramine by its agent, and the sample actually contained sibutramine as shown by chemical analysis. According to purported country of marketing authorization holder, 25 sibutramine products originated from India (dispatched from India, Hong Kong and Fiji Islands), seven from China (dispatched from China), seven from Germany (dispatched from Hong Kong and Cambodia) and three from Hong Kong (dispatched from Cambodia). Among 15 orlistat products, seven originated from India (dispatched from India and Japan), five from United Kingdom (dispatched from Switzerland, USA and Japan), two from Switzerland (dispatched from Puerto Rico) and one from Thailand (dispatched from Thailand). Two rimonabant, benfluorex and one lovastatin samples originated from India (dispatched from Thailand and Japan), France (dispatched from Hong Kong) and USA (dispatched from USA) respectively. All herbal products (including daidai hua) originated from China, except two (i.e.: *Pachyma hoelen*), which are from USA, however, dispatched from China.

## Quality analysis



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Out of total, 52 samples (i.e.: Sibutramine: 21, Orlistat: 13, Rimonabant: 2, Benfluorex: 2, Lovastatin: 1 and herbal products: 13) were analyzed by HPLC to measure quantity of active ingredients in the samples. Thirty samples (received in divided shipments and identical with an analyzed sample from a same source respectively) were excluded because of the insufficient materials. Quantitative analysis by HPLC showed that all (21) of the samples of sibutramine were in the acceptable range (90%-110%) except one (mean content percentage of 60.2±7.6). No active ingredient was detected in three out of the 13 samples of orlistat that we tested (Figure 1). These three samples were identified to be counterfeit. Of these three counterfeit samples, two were found to be Xenical after analysis by the researchers and the manufacturer of the genuine products. No active ingredient was detected in the last sample, only starch (Figure 1). The other counterfeit sample contained unknown excipients. None of the samples of lovastatin, benfluorex or rimonabant failed the HPLC analysis.

**Authenticity investigation**

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

(Table 24).

Table 24. Results of Authenticity Investigation

Active ingredient	<del>Labeled c</del> <del>Country of</del> <del>Authorized m</del> <del>Marketing</del> <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

\* labeled manufacturer did not reply

The counterfeit samples were purchased at [www.kenkoclinic.com](http://www.kenkoclinic.com) and sent to us from Puerto Rico. They bore the same manufacture and expiration dates (MFD: 02/2011 and EXP: 02/2011,

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340 Figure 2) on their blisters, which had not yet occurred at the time of our investigation. The  
341 printed information on the blisters of the counterfeits was a different color with a similar but  
342 slightly different logo (Figure 3).

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344 Telephone communications were made to the manufacturer of Zenigal (orlistat 120 mg) in India,  
345 which did not contain any of the active ingredients that had been claimed on the product labels.  
346 However, the manufacturer did not respond after several communication attempts. This  
347 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of  
348 counterfeit medicines at the rapid alert system of the Western Pacific Region of the World  
349 Health Organization.

350  
351 Responses were received from the medical regulatory authorities of three countries (Germany,  
352 Switzerland and USA) for five of the manufacturers. Their responses stated that only orlistat has  
353 approval to be manufactured in Switzerland. Approval for the manufacture of sibutramine in  
354 Germany was suspended in January 2010, and it was not approved for use in the USA.

355

356 **DISCUSSION**

357 **Provided information on the samples**

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

### Approval status of the products

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

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weight,<sup>[45][26]</sup> However, after conclusion of the safety review of sibutramine, the European  
Medicines Agency (EMA) has suspended its marketing authorization in the European Union  
(EU),<sup>[46][27]</sup> A recently published study reported that generic Figurer (sibutramine 10 mg),  
even though it has not been reviewed by the responsible government (USA, the exporting  
nation), is freely circulating via the Internet, which is a serious concern for public  
health,<sup>[35][22]</sup> According to the medicine regulations of Hong Kong, Figurer does not need  
manufacturing authorization because the medicine is manufactured in a foreign country. The  
authorization status of Ali (orlistat 60 mg) as a prescription medicine has been recommended to  
transition to a non-prescription medicine in the EU,<sup>[47][28]</sup> In a questionnaire conducted by  
community pharmacists in Great Britain, orlistat is suspected to be misused by consumers, as  
stated in their responses,<sup>[48][29]</sup> Similarly, marketing authorization for Acomplia (rimonabant)  
has also been withdrawn in the EU in January 2009 and safety profiles of other anti-obesity  
agents are generating controversy in different parts of the world,<sup>[49-53][30-33]</sup> Even though all  
the anti-obesity agents sampled in this survey are unapproved in Japan, it is possible that anyone  
can procure these items without declaring the actual contents during shipping.

**Authenticity and quality of the samples**

As similarly shown in previous studies, we observed low rates of authenticity,<sup>[54][34]</sup>

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

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

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

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

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

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

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

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

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

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

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

consumption of fake or substandard medicines purchased online.<sup>[59][40]</sup> When products are

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

accept the consequences.

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

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

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

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412 million.[60] Nevertheless, PAL has only jurisdiction to regulate domestic traders and has no  
413 hold on foreign online traders. Strengthening international collaboration along with  
414 public-private partnership initiatives may facilitate stemming out illegal internet trading hosted  
415 from outside national boundaries.[19, 61, 62]

417 One of the limitations of the study might be small sample size, which may restrict study  
418 findings to Japan. The sampling scheme may also limit our findings from generalization to all  
419 internet sites. However, the sampling scheme was purposefully designed to investigate  
420 suspicious online medicine sites. Our study was not designed comprehensively to explore  
421 information during shipment of medicinal products especially at Japanese custom check.  
422 Further evaluation with a representative sample may provide more information on the extent of  
423 the problem. Low response rate of authenticity investigation may also be considered as a  
424 limiting factor. However, better communication and cooperation among authentic manufacturers  
425 and medicine regulatory authorities may increase response rate and generate more information  
426 to counteract against counterfeits.

428 **CONCLUSIONS**

429 It is evident from this study that counterfeit, unapproved and suspended anti-obesity medicines

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are circulating via the Internet. Because of gaps and the insufficient monitoring system of imports for personal use in the rapidly growing e-commerce environment, these medicines can easily enter into the distribution channels for pharmaceuticals and may pose health hazards for consumers. Time has come to address such gaps of cross-border pharmaceutical e-commerce and regulate the same through international cooperation and public-private partnerships. Obviously, first and foremost step should be at country levels to make necessary amendments of existing regulation focusing online pharmaceutical transactions. Furthermore, there might be an urgent need at international level to formulate common regulation and agreements focusing issues of pharmaceutical e-commerce.

—

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**Competing interests** The authors declare no conflict of interest.



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450 **Authors' contribution** MHK, TT, YN, and KK participated in the conception and design of the  
451 study; TT, YN and KK participated in sampling activities and analysis of the samples; MHK, TT,  
452 YN, NY, HT and KK participated in data analysis and interpretation of results. MHK wrote the  
453 first draft of the manuscript. All authors contributed in the critical review of the draft manuscript,  
454 editing and finally approved its submitted version.

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457 **Data sharing statement** No additional data available.

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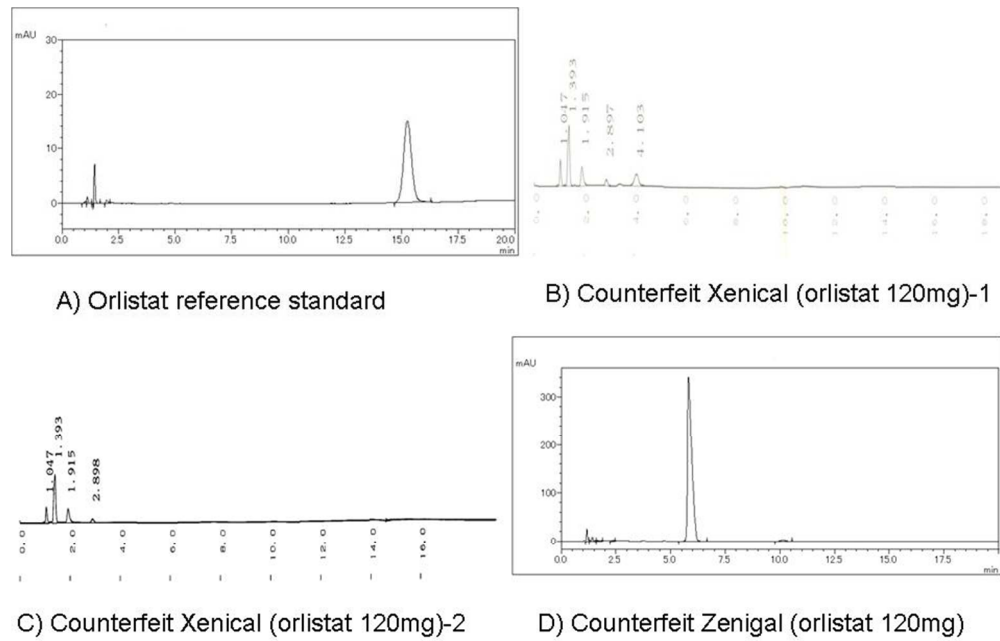


Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples  
254x190mm (96 x 96 DPI)

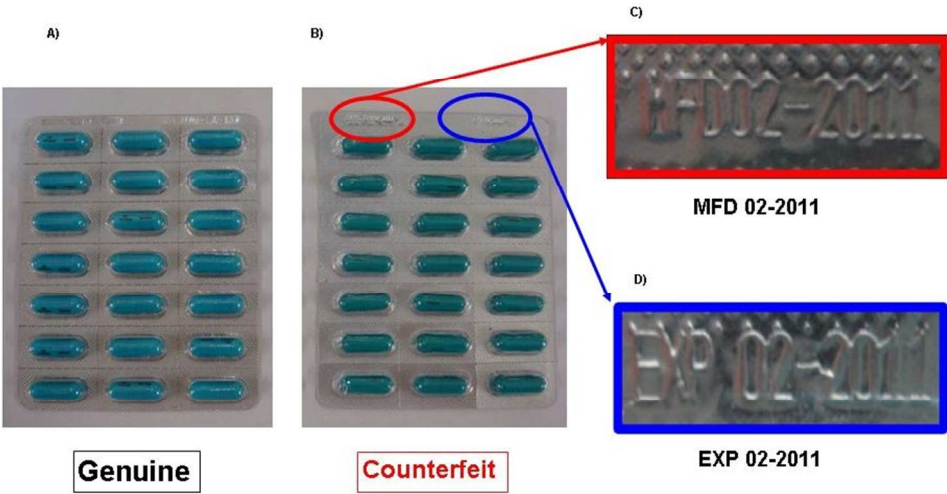


Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)  
254x190mm (96 x 96 DPI)



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
Introduction			
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
Methods			
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.
Results			

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).



## Correction

Khan MH, Tanimoto T, Nakanishi Y, *et al.* Public health concerns for anti-obesity medicines imported for personal use through the internet: a cross-sectional study. *BMJ Open* 2012;**2**:e000854. The captions for figures 1C and 1D should be “Counterfeit Zenigal (orlistat 120 mg)” and “Counterfeit Xenical (orlistat 120mg)-2” respectively. The authors apologise for this error.

*BMJ Open* 2012;**2**:e000854corr1. doi:10.1136/bmjopen-2012-000854corr1