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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000854
Article Type:	Research
Date Submitted by the Author:	11-Jan-2012
Complete List of Authors:	Khan, Mohiuddin; Kanazawa University, Drug Management and Policy Tanimoto, Tsuyoshi; Doshisha Women's College, Nakanishi, Yoko; Public Health Center, ; Kanazawa University, Drug Management and Policy Yoshida, Naoko; Kanazawa University, Drug Management and Policy Tsuboi, Hirohito; Kanazawa University, Drug Management and Policy Kimura, Kazuko; Kanazawa University, Drug Management and Policy
Primary Subject Heading:	Public health
Secondary Subject Heading:	Global health, Pharmacology and therapeutics, Nutrition and metabolism
Keywords:	PUBLIC HEALTH, NUTRITION & DIETETICS, MEDICAL LAW, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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

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Running title: Quality of online anti-obesity medicines

Word counts: 3,088

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 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. Three of the samples were identified as counterfeits and did not contain any active ingredients according to the chemical analyses. Two of these samples were confirmed as counterfeits by the manufacturer of the authentic products. The manufacturer of the other sample did not respond to our request for

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

Conclusion: Many counterfeit and unapproved anti-obesity medicines may be easily bypassing regulatory checks during shipping and are widely circulated through the Internet. Regulatory authorities should take measures to prevent these medicines from entering countries to 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.

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 utilize the Internet for their health related activities.[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 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.[3] However, according to World Health Organization, more than 50% of the medicines from Internet sites, which often conceal their physical address, may be counterfeit or of substandard quality.[4]

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.[5] The prevalence of obesity and its associated conditions are increasingly affecting both developed and developing countries over the last few decades.[6] Studies suggest that primarily adolescent and adult males are overweight or obese in Japan.[7] Recommended strategies for managing weight and obesity include lifestyle changes with appropriate dietary management and exercise. However, individuals with an isolated BMI≥30

kg m^{-2} or a BMI>27 kg m^{-2} with co-morbidities such as type 2 diabetes, cardiovascular diseases, and obstructive sleep apnea, should receive pharmacotherapy as well.[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.[9, 10] Of these anti-obesity medicines, only mazindol has been approved for use in Japan.[11] However, several of these anti-obesity medicines are among those that are frequently imported into Japan for personal use.[12]

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.[4, 13-15] 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.

METHODS

Study design

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

Selection of Internet sites and sample collection

The Japanese keywords personal import agent, diet, and anti-obesity medicines were used on the Japanese Google search engine (www.google.co.jp) to find online pharmacies or suppliers that offer anti-obesity medicines. Searches were also made on websites that advertise and sell counterfeit Cialis, Levitra and Viagra. 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] 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 medicines according to their vertical or horizontal placement on the web pages. 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.

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, Japanese manual, 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 were established and performed

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

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 subsequently weighed. The difference between the weight of the whole capsule and the capsule shell was assumed to be the weight of the contents. Approximately 80 ml of methanol was added to the capsule's contents, 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 mg and 1.50 mg of orlistat; 0.050 mg, 0.100 mg and 0.200 mg of sibutramine; 0.100 mg, 0.200 mg and 0.500 mg of lovastatin; 0.100 mg, 1.50 mg and 2.00 mg of benfluorex; 0.100 mg, 0.200 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.

Assay condition

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

Authenticity investigation

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

appropriate manufacturers with a portion of the samples for verification of their authenticity. The regulatory authorities for medicine in the country of origin were also contacted to verify the 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.[17, 18]

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. 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.

Information available on the web sites

Different levels of compliance with ASCT were observed throughout all (36) of the web sites. 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 17.1% of the samples, Chinese for 15.9%, both Chinese and Korean for 12.2%, both English and Chinese for 4.9%, Turkish for 2.4%, both English and Thai for 1.2%, and English, Chinese and Russian for 1.2% of the samples. However, 45.1% (37) 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 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 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, 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±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 1).

Table 1. Results of Authenticity Investigation

Active ingredient	Country of Authorized Marketer	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 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 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of counterfeit medicines at the rapid alert system of the Western Pacific Region of the World Health Organization.

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

DISCUSSION

Provided information on the samples

According to the Pharmaceutical Affairs Law 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.[19] 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.[20] 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.[19] As found in many previous studies on e-medicines, approximately 50% of the samples did not contain a package insert.[21-25] Moreover, several of the weight-loss products may contain harmful or contraindicated ingredients.[16, 21]

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 weight.[26]

However, after conclusion of the safety review of sibutramine, the European Medicines Agency (EMEA) has suspended its marketing authorization in the European Union (EU).[27] 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.[22] 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.[28] In a questionnaire conducted by community pharmacists in Great Britain, orlistat is suspected to be misused by consumers, as stated in their responses.[29] Similarly, safety profiles of other anti-obesity agents are generating controversy in different parts of the world.[30-33] 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.[34] 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.[35, 36] 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.[37, 38] As shown in some other studies, the counterfeits detected in this survey did not contain any active ingredients.[34, 39] 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.[40] When products are purchased through the Internet and the sites are not sufficiently regulated, customers are left to accept the consequences.

One of the limitations of the study might be small sample size, which may restrict study findings to Japan. 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.

Acknowledgements We gratefully acknowledge the cooperation received from the staff of MHLW. Additionally, we thank Ms. Hitomi Tabata for her cooperation in this work.

Funding This study was supported by Health and Labour Sciences Research Grants from the MHLW, Japan.

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.

Data sharing statement No additional data available.

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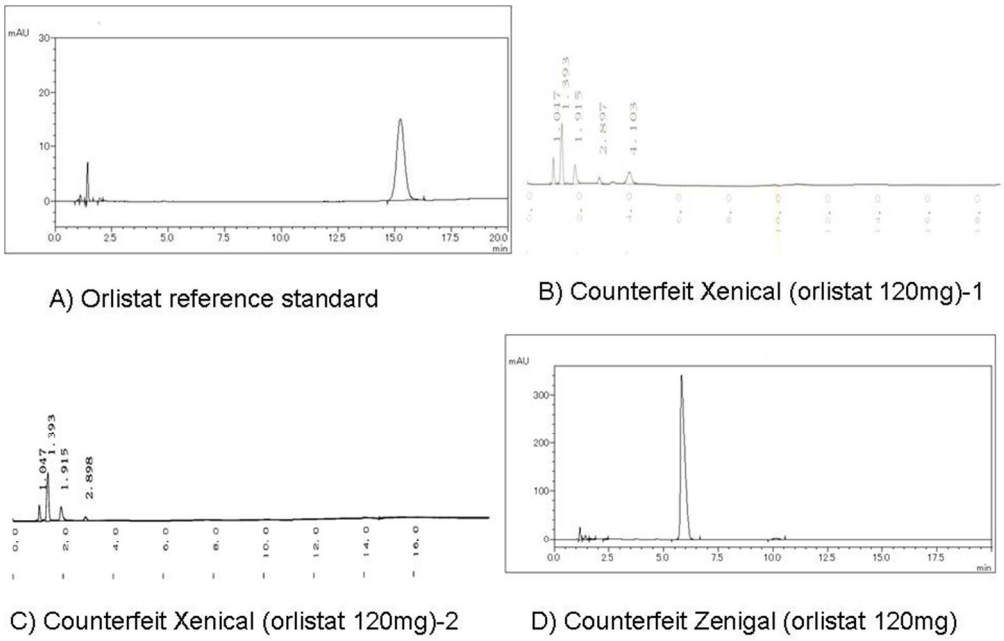

Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples
254x190mm (96 x 96 DPI)

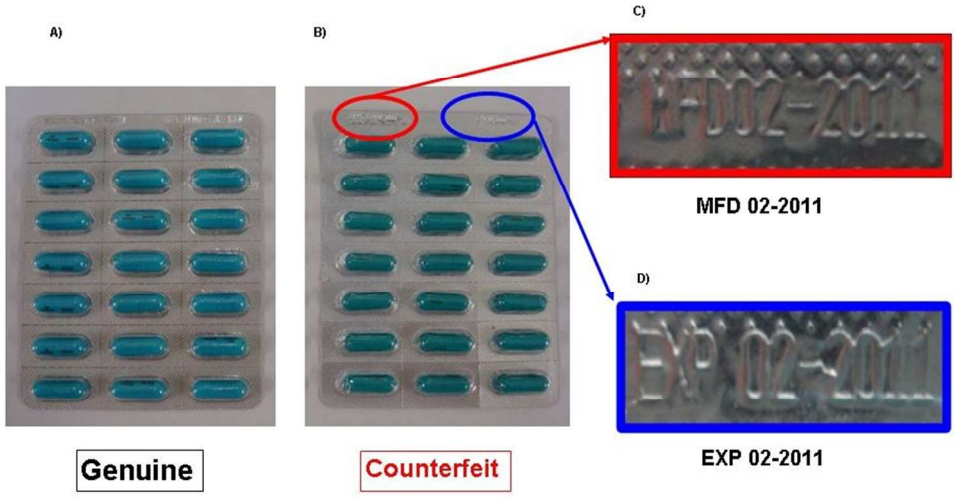

Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)
254x190mm (96 x 96 DPI)

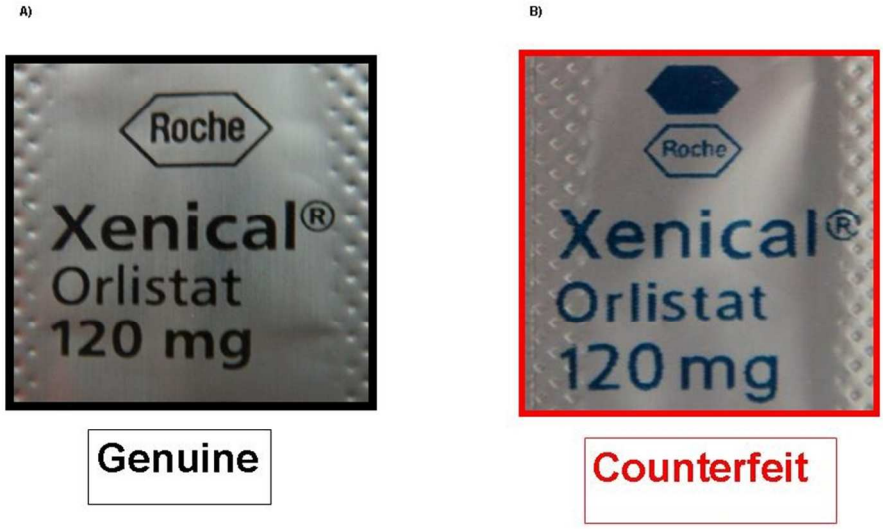

Figure 3. Reverse side of blister: A) Logo of genuine sample, B) Logo of counterfeit sample
254x190mm (96 x 96 DPI)

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
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.

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

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

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

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Running title: Quality of online anti-obesity medicines

Word counts: 3,996~~088~~

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~~urvey~~.

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 pharmcopoeial quality. Authenticity responses were received from only five out of 20 manufacturing companies. According to pharmacopoeial analyses and authenticity investigation, t~~T~~hree of the samples were identified as counterfeits and

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

Conclusion: Many counterfeit and unapproved anti-obesity medicines may be easily bypassing regulatory checks during shipping and are widely circulated through the Internet. Regulatory authorities should take measures to prevent these medicines from entering countries to 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.

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]

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≥30 kg m^{-2} or a BMI>27 kg m^{-2} 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~~urvey~~ during August 2009.

Selection of Internet sites and sample collection

Internet sites were selected in five steps to purchase anit-obesity medicines. In the first step, ~~T~~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, ~~S~~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~~

~~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, packageing 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, talemarketing 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

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 mg and 1.50 mg of orlistat; 0.050 mg, 0.100 mg and 0.200 mg of sibutramine; 0.100 mg, 0.200

mg and 0.500 mg of lovastatin; 0.100 mg, 1.50 mg and 2.00 mg of benfluorex; 0.100 mg, 0.200 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.

Assay condition

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

Authenticity investigation

A catalogue and a questionnaire for all the samples were created that included the information from the printed labels of the product packages. The printed information was also checked against the information on the manufacturers' websites. The questionnaires were sent to the appropriate manufacturers with a portion of the samples for verification of their authenticity. The regulatory authorities for medicine in the country of origin were also contacted to verify the 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.[7, 36]~~[17, 18]~~

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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 medici

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Orlistat	Not approved	15 (18.3)	Prescription medicine: 10 Over the counter: 5*
Rimonabant	Not approved	2 (2.4)	Prescription medicine
Benfluorex	Not approved	2 (2.4)	Prescription medicine
Lovastatin**	Not approved	2 (2.4)	Prescription medicine
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), **: 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.[35] 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~~% %(37~~) 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 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

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, 42~~3~~ (51~~2~~.2~~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 1~~8~~7 (2~~1~~0.9~~7~~%) 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. ~~f~~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 Camboida). 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±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 2~~1~~).

Table 2~~1~~. Results of Authenticity Investigation

Active ingredient	Labeled c~~C~~ountry of ~~Authorized~~ m~~M~~arketing	Genuine sample	Counterfeit sample	Manufacturing License

	authorization holder~~er~~			
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 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

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

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

DISCUSSION

Provided information on the samples

According to the Pharmaceutical Affairs Law 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.[37][~~19~~] 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.[35]~~[20]~~ 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.[37]~~[19]~~ As found in many previous studies on e-medicines, approximately 50% of the samples did not contain a package insert,[38-42]~~[21-25]~~ Moreover, several of the weight-loss products may contain harmful or contraindicated ingredients,[33, 38]~~[16, 21]~~ Similar to the findings of a recent study, none of the websites of our study required a prescription to purchase medicines.[43, 44]

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 weight.[45]~~[26]~~ However, after conclusion of the safety review of sibutramine, the European Medicines Agency (EMEA) has suspended its marketing authorization in the European Union (EU).[46]~~[27]~~ 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.[39]~~[22]~~ According to the medicine regulations of Hong Kong, Figurer does not need 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.[47][~~28~~] In a questionnaire conducted by community pharmacists in Great Britain, orlistat is suspected to be misused by consumers, as stated in their responses.[48][~~29~~] 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.[49-53][~~30-33~~] 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.[54][~~34~~] 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.[55, 56][~~35, 36~~] 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.[17, 57][~~37, 38~~] As shown in some other studies, the counterfeits detected in this survey did not contain any active ingredients.[54, 58][~~34, 39~~] 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.[59]~~[40]~~ 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.[60] In case of such violation by a company, the penalty may be increased to maximum JP¥ 100 million.[60] 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.[19, 61, 62]

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.

Acknowledgements We gratefully acknowledge the cooperation received from the staff of MHLW. Additionally, we thank Ms. Hitomi Tabata for her cooperation in this work.

Funding This study was supported by Health and Labour Sciences Research Grants from the MHLW, Japan.

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.

Data sharing statement No additional data available.

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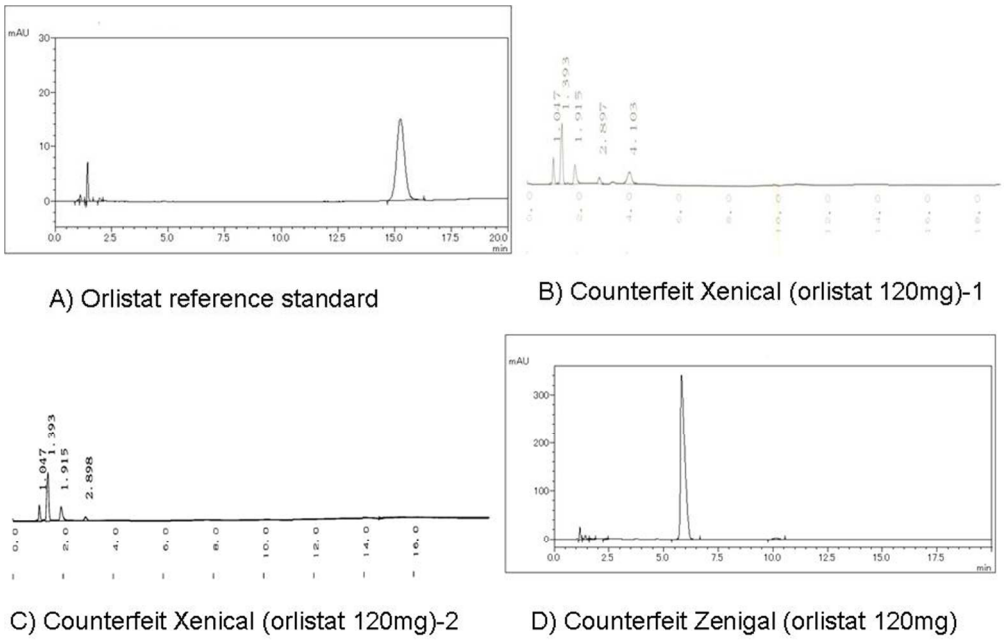

Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples
254x190mm (96 x 96 DPI)

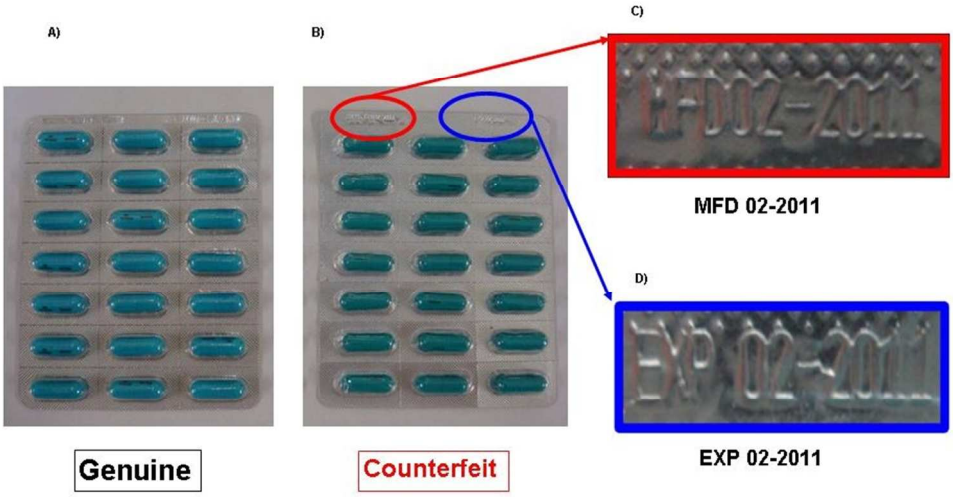

Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)
254x190mm (96 x 96 DPI)

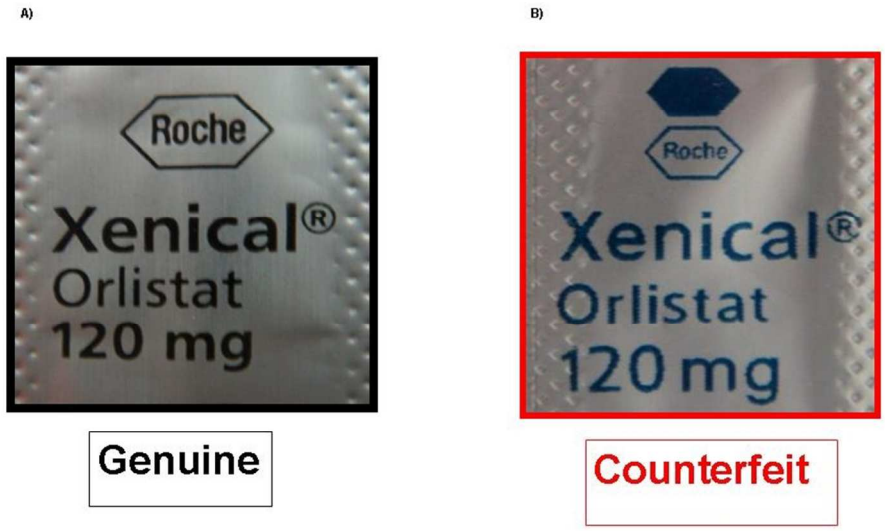

Figure 3. Reverse side of blister: A) Logo of genuine sample, B) Logo of counterfeit sample
254x190mm (96 x 96 DPI)

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
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.

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

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

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

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Running title: Quality of online anti-obesity medicines

Word counts: ~~3,~~3992~~088~~

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~~urvey~~.

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 pharmcopoeial quality. Authenticity responses were received from only five out of 20 manufacturing companies. According to pharmacopoeial analyses and authenticity investigation, t~~T~~hree of the samples were identified as counterfeits and

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

Conclusion: Many counterfeit and unapproved anti-obesity medicines may be easily bypassing regulatory checks during shipping and are widely circulated through the Internet. Regulatory authorities should take measures to prevent these medicines from entering countries to 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.

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.[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 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≥30 kg m^{-2} or a BMI>27 kg m^{-2} 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]

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 was 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 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, an 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~~urvey~~ during August 2009.

Selection of Internet sites and sample collection

Internet sites were selected in five steps to purchase anit-obesity medicines. In the first step, ~~T~~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. Websites with physical address and/or blogs and advertise-only sites were excluded in this step. In the second through fourth steps, ~~S~~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). From our experiences on previous online medicine studies, we presumed that the websites offer counterfeit ED drugs,

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, talemarketing 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]

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 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

mg and 1.50 mg of orlistat; 0.050 mg, 0.100 mg and 0.200 mg of sibutramine; 0.100 mg, 0.200 mg and 0.500 mg of lovastatin; 0.100 mg, 1.50 mg and 2.00 mg of benfluorex; 0.100 mg, 0.200 mg and 0.500 mg of rimonabant in 1 ml of methanol for each solution.

Assay condition

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

Authenticity investigation

A catalogue and a questionnaire for all the samples were created that included the information from the printed labels of the product packages. The printed information was also checked against the information on the manufacturers' websites. The questionnaires were sent to the appropriate manufacturers with a portion of the samples for verification of their authenticity. The regulatory authorities for medicine in the country of origin were also contacted to verify the

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.[7, 37]~~[17, 18]~~

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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: 10 Over the counter: 5*
Rimonabant	Not approved	2 (2.4)	Prescription medicine
Benfluorex	Not approved	2 (2.4)	Prescription medicine
Lovastatin**	Not approved	2 (2.4)	Prescription medicine
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.

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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~~% %(37~~) 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

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 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, 42~~3~~ (51~~2~~.2~~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 18~~7~~ (21~~0~~.9~~7~~%) 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. ~~f~~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 Camboida). 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 (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 2~~1~~).

Table 2~~1~~. Results of Authenticity Investigation

Active ingredient	Labeled c~~C~~ountry of ~~Authorized~~ m~~M~~arketing authorization holder~~er~~	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 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 counterfeit Zenigal sample was sent to us from Japan. We reported these three cases of counterfeit medicines at the rapid alert system of the Western Pacific Region of the World Health Organization.

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

DISCUSSION

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.[38]~~[19]~~ 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.[36]~~[20]~~ 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.[38]~~[19]~~ As found in many previous studies on e-medicines, approximately 50% of the samples did not contain a package insert.[35, 39-42]~~[21-25]~~ Moreover, several of the weight-loss products may contain harmful or contraindicated ingredients.[33, 39]~~[16, 21]~~ Similar to the findings of a recent study, none of the websites of our study required a prescription to purchase medicines.[43, 44]

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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

weight.[45][~~26~~] However, after conclusion of the safety review of sibutramine, the European Medicines Agency (EMEA) has suspended its marketing authorization in the European Union (EU).[46][~~27~~] 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.[35][~~22~~] 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 Alli (orlistat 60 mg) as a prescription medicine has been recommended to transition to a non-prescription medicine in the EU.[47][~~28~~] In a questionnaire conducted by community pharmacists in Great Britain, orlistat is suspected to be misused by consumers, as stated in their responses.[48][~~29~~] 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.[49-53][~~30-33~~] 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,[54][~~34~~]

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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.[55, 56][~~35, 36~~] 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.[17, 57][~~37, 38~~] As shown in some other studies, the counterfeits detected in this survey did not contain any active ingredients.[54, 58][~~34, 39~~] 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.[59][~~40~~] When products are purchased through the Internet and the sites are not sufficiently regulated, customers are left to accept the consequences.

According to the 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.[60] In case of such violation by a company, the penalty may be increased to a maximum JP¥ 100

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million.[60] 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.[19, 61, 62]

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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 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 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.

Acknowledgements We gratefully acknowledge the cooperation received from the staff of MHLW. ~~Additionally, we thank Ms. Hitomi Tabata for her cooperation in this work.~~

Funding This study was supported by ~~Health and Labour Sciences~~ Research Grants from the MHLW, Japan.

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.

Data sharing statement No additional data available.

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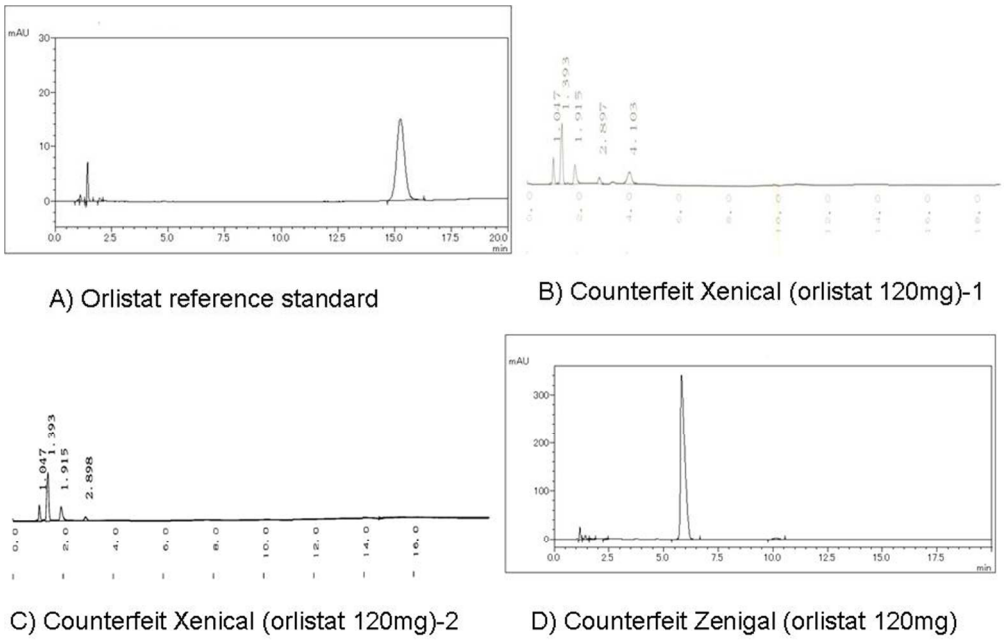

Figure 1: Chromatograms of the reference standard of orlistat and counterfeit samples
254x190mm (96 x 96 DPI)

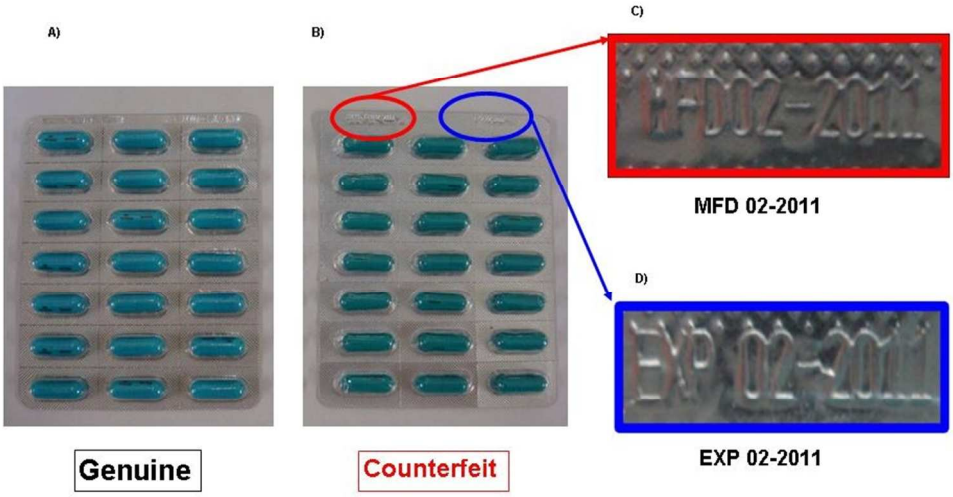

Figure 2. Front of blister: A) Genuine sample, B) Counterfeit sample, C) Manufacturing date of counterfeit sample (MFD 02-2011), D) Expiration date of counterfeit sample (EXP 02-2011)
254x190mm (96 x 96 DPI)

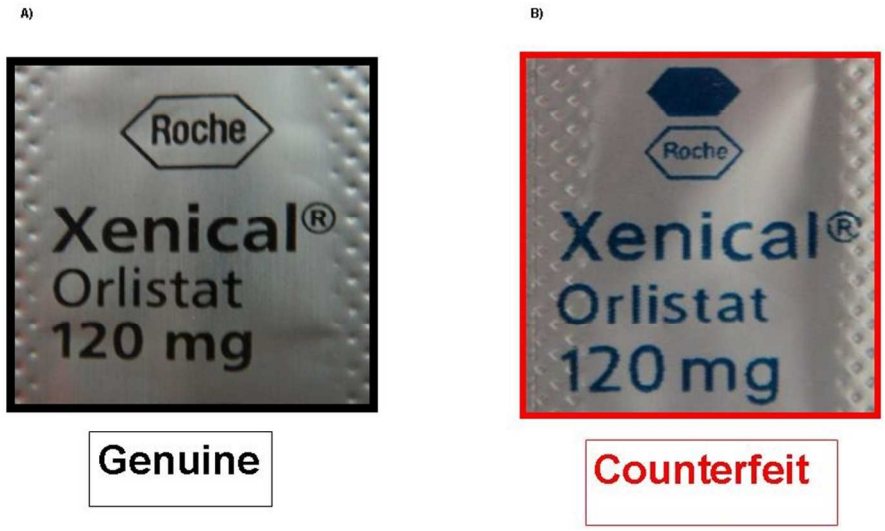

Figure 3. Reverse side of blister: A) Logo of genuine sample, B) Logo of counterfeit sample
254x190mm (96 x 96 DPI)

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
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.

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