Medicine Access @ Point of Care
2021, Volume 5: 1–8

DOI: 10.1177/23992026211002089
journals.sagepub.com/home/map
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Quality assessment of Diflucan® tablets distributed online: Diflucan® distributed online

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Abstract

Background: Falsified medical products have been reported worldwide. Falsified medicines with poor quality are a potential health hazard. Some Internet sites advertise fluconazole (Diflucan®), an antifungal medicine used to treat deep mycoses, as "female Viagra®."

Aim: The aim of this study was to investigate the authenticity and quality of Diflucan® tablets distributed on the Internet.

Methods: We ordered Diflucan® tablets via the Internet and evaluated them by visual observation, authenticity investigation, quality evaluation (quantity of the active pharmaceutical ingredient, content uniformity, and dissolution), and near-infrared and Raman scattering spectroscopy.

Results: We obtained 11 samples of Diflucan® tablets from all 11 Japanese Internet sites identified in our search. Of 11 sites, 7 advertised fluconazole as having effects on female sexual function. Ten of the Diflucan® samples were confirmed as genuine and one sample was falsified. The genuine Diflucan® samples met the specifications of all quality evaluations. The packaging, size, and color of the falsified Diflucan® sample obtained in this study differed from the authentic Diflucan® tablet. The falsified Diflucan® sample obtained in this study did not contain fluconazole and instead contained what appeared to be sildenafil citrate. The spectra of the falsified Diflucan® tablet obtained in this study differed from the authentic Diflucan® tablet in near-infrared and Raman scattering spectroscopy.

Conclusion: We confirmed that one falsified Diflucan® tablet was distributed online. Thus, continued measures against falsified medicines are required.

Keywords

falsified medicines, patient safety, Diflucan®, fluconazole, female Viagra®, sildenafil citrate, identification

Date received: 19 February 2021; accepted: 23 February 2021

Introduction

The World Health Organization (WHO) has defined "falsified" medical products as those that are intentionally mislabeled, as opposed to substandard and unregistered or unlicensed products.[1] "Substandard" medical products are authorized products that do not meet the quality standard, whereas "unregistered/unlicensed" medical products have not been approved for market under the governing regulations and legislation. According to the Organization for Economic Co-operation and Development, trade in falsified goods, including medicines, is on the rise.[2] Substandard and falsified medicines are spread around the world, with

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one-tenth of medicines in low- and middle-income countries (LMICs) reported to be substandard or falsified. According to the WHO Global Surveillance and Monitoring System for substandard and falsified medical products, there were approximately 1500 reports of substandard and falsified medicines from 2013 to 2017; with regard to class, the highest number of falsified products were systemic anti-infective medicines.[3] The WHO also reported that an estimated 31,000–116,000 people died from substandard or falsified antimalarial drugs in sub-Saharan Africa in 2019.[4] In addition, substandard and falsified medicines are not only a problem in LMICs; falsified anticancer and anti-HIV drugs have been reported in the United States and Europe.[5–7] Falsified medicines lead to health hazards and people's loss of medical confidence. Furthermore, as Internet commerce has flourished, individuals have more opportunities to purchase medicine online, leading to easy access to falsified medicine and the subsequent health problems involved.[8–10] In Japan, online pharmacies selling prescription medicines are not approved, but it is not illegal to import medicines via the Internet for the purpose of continuing medical treatment started in foreign countries or if they are carried by foreigners as regular medicines.[9] The Japanese Ministry of Health, Labor, and Welfare has warned its citizens of the risks of falsified products obtained by personal import.[10] Personal import is one of the main inflow routes of falsified medicines into Japan, as we reported in previous studies.[11–15] Pharmaceutical companies attempt to decrease the counterfeiting of medicines by securing supply chains and collaborating with governmental agencies to control the availability of falsified products.[16] Spectroscopic analysis, such as near-infrared (NIR) spectroscopy and Raman scattering spectroscopy, have been leveraged to detect falsified medicines as types of non-destructive analyses.[17–21]

Fluconazole, an antifungal agent widely used for the treatment of deep mycoses, is sold by Pfizer Inc. (New York, NY, USA) under the brand name Diflucan®. As shown by an Internet search for fluconazole tablets, several sites are advertising fluconazole as "female Viagra®." Viagra® is a medicine for erectile dysfunction that contains sildenafil citrate as an active pharmaceutical ingredient. On these sites, fluconazole is described as having the ability to maintain genital moisture in addition to an antifungal effect, although fluconazole has not been medically approved for an effect on sexual function. Although previous reports indicated the existence of falsified Diflucan® tablets and low-quality fluconazole products,[15,22–25] details such as the appearance and ingredients of falsified fluconazole products have not been revealed.

In this study, we investigated the authenticity and quality of Diflucan® tablets distributed on the Internet. Here, we report the results of this survey with reference to guidelines for field survey of the quality of medicines.[26,27]

Materials and methods

Nature of the study

This study was a survey of medicines available in the online market.

Materials

We obtained genuine 100 mg Diflucan® tablets from Pfizer as the standard. Acetonitrile, methanol, sodium acetate trihydrate, glacial acetic acid, formic acid, and a reference standard for fluconazole were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Ammonium formate was purchased from Nacalai Tesque, Inc. (Kyoto, Japan). A reference standard for sildenafil citrate was purchased from the United States Pharmacopeia (Rockville, MD, USA). A fluconazole reference standard was used to generate the calibration curve for quality evaluations.

Sample collection

Samples were collected according to methods reported in previous studies.[12–14,28,29] We searched for fluconazole tablets on the Japanese Google search engine using the keywords "fluconazole and personal import (フルコナゾール AND 個人輸入)." We selected 100 mg Diflucan® tablets because falsified tablets of this dosage had previously been reported.[15] We ordered products from all Japanese sites extracted by keyword search. There was no randomization process to select sites. Products were ordered between 26 August and 12 November 2014. We ordered the smallest number of tablets over 28 tablets from each site to obtain samples from as many sites as possible.

Authenticity investigation

A questionnaire with photographs and tablets of all samples were sent to the manufacturer of Diflucan® tablets, Pfizer, for authentication. The questionnaire, which is included as supplementary file, contained content related to authenticity that could only be judged by the manufacturer; surveys conducted using similar questionnaire were previously reported.[12–14,28,29]

Price

We calculated the price per tablet of the samples. We compared the prices of genuine and falsified samples because customers are concerned about price and it is a selection factor on purchasing sites.

Visual inspection

We conducted a visual inspection of the products received according to the International Pharmaceutical Federation

checklist.[30] Tablet size of three tablets per sample was measured using a digital micrometer (MCD 130-25, Niigata Seiki Co., Ltd., Niigata, Japan). Because Diflucan® tablets are trapezoid, the width of the long side was measured. Tablet color was measured by spectrocolorimetry (CR-300, Konica Minolta Japan, Inc., Tokyo, Japan). As a control, one standard Diflucan® tablet was measured 10 times, and each sample tablet was measured five times. The average value was calculated for each tablet. Lightness (L^*) and chromaticity (a^*, b^*) values were measured and $\Delta E^*ab = ((\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2)^{1/2}$ was calculated using the average of each value. Differences in color were assessed by the value of ΔE^*ab.[31]

Quantity and content uniformity test

Quantity, content uniformity, and dissolution were evaluated according to the United States Pharmacopeia (USP) 37th edition.[32] The content of the active pharmaceutical ingredient was measured with a high-performance liquid chromatography (HPLC) system equipped with a photodiode array detector (PDA) (JASCO Corporation, Tokyo, Japan). The wavelength was 261 nm and the column was a Nova-Pak C18 (4 μm, 3.9 mm × 150 mm; Nihon Waters K.K., Tokyo, Japan), which was maintained at 40°C. The mobile phase was methanol-acetonitrile-anhydrous sodium acetate solution (pH 5.0; 0.01 M) (20:10:70, v/v/v). The flow rate was 1.0 mL/min and the injection volume was 20 μL. One tablet was dissolved in purified water to make 100 mL, and sonicated for 30 min. The mobile phase was added to 2 mL of the solution to make 10 mL, and sonicated for 30 min.

Dissolution was checked using a paddle apparatus (NTR-VS6 P, Toyama Sangyo Co. Ltd., Osaka, Japan). The paddle rotation speed was set to 50 rpm and the temperature was maintained at 37 ± 0.5°C. Each tablet was added to 900 mL of purified water and dissolved for 45 min. In this study, dissolution was tested with three tablets per sample. Dissolution test of six tablets was judged as a "pass" when the dissolution rate was 80% or more.[32]

Identification of sildenafil citrate

We modified a previous method,[11,12] and used an HPLC system equipped with a PDA (Shimadzu Corporation, Kyoto, Japan) to record ultraviolet spectra from 200 to 400 nm. The column was a Shim-pack CLC-ODS (4.6 mm × 150 mm; Shimadzu GLC Ltd., Tokyo, Japan), which was maintained at 40°C. Mobile phase A was 20 mM ammonium formate-0.2% formic acid (1:1, v/v), and mobile phase B was acetonitrile. The gradient conditions were 80% A and 20% B (0 min), 50% A and 50% B (20–25 min), and 80% A and 20% B (28–40 min). The flow rate was 1.0 mL/min, and the injection volume was 20 μL.

Spectroscopy

Near-infrared spectroscopy was carried out using a portable apparatus (microPHAZIR-GP; Thermo Fisher Scientific, Waltham, MA, USA). Each tablet was measured five times and the measurement time was 3.0 s or less. We used two analyzers to measure Raman scattering on the surface of the Diflucan® tablets. The instruments differed in size, measurement wavelength, and performance. The first and large one was a Raman triple grating spectrometer (T64000; Horiba, Ltd., Kyoto, Japan). The standard Diflucan® tablet from the manufacturer and genuine tablets were measured three times with an exposure time of 10 s, and falsified tablets were measured five times with an exposure time of 1 s. The wavelength was 659.47 nm and the power was 50 mW. The Raman triple grating spectrometer had high accuracy but required installation. The other analyzer was a portable Raman scattering analyzer (Inspector 500; SciAps, Inc., Woburn, MA, USA), which was handheld, small, and easy to operate. Each tablet was measured five times with an automatic exposure time (maximum 8.0 s). The wavelength was 1030 nm and the power was 300 mW. Dimensions of the analyzer were 190 mm × 176 mm × 44 mm, and the instrument weighed 1.7 kg.

Results

Sample collection

A total of 11 Japanese websites sold Diflucan® tablets, and none requested a prescription. We ordered 100 mg Diflucan® tablets from all 11 sites, and the products were received between 3 September and 9 December 2014. Sample information is shown in Table 1. One website shipped 200 mg Diflucan® tablets even though we had ordered 100 mg tablets. All products were shipped in bottles that had labels listing the United States as the country of manufacture. For 10 samples, the shipping country listed on the postal label was the United States. There was no shipping source information on the package of Sample No.10, although a Japanese stamp was present on the envelope. Package inserts in English were included in nine cases. Of the 11 websites, 7 advertised the product to have effects on female sexual function, and 1 of 7 sites advertised the product as "female Viagra®"; however, there was no mention of sexual effects on the products we obtained from these sites.

Authenticity investigation

The manufacturing company, Pfizer, completed questionnaires regarding the authenticity of all samples (Table 1). Of 10 Diflucan® samples (100 mg), 9 were genuine, but the 10th was falsified. The 200 mg Diflucan® sample was also genuine.

Table 1. Sample details and authenticity.

Sample No.	Dose (mg)	Manufacturing country listed on label	Shipping country listed on label	Package insert	Sample authenticity
1	100	USA	USA	English	Genuine
2	100	USA	USA	English	Genuine
3	100	USA	USA	English	Genuine
4	100	USA	USA	English	Genuine
5	100	USA	USA	English	Genuine
6	100	USA	USA	English	Genuine
7	100	USA	USA	None	Genuine
8	100	USA	USA	English	Genuine
9	100	USA	USA	English	Genuine
10	100	USA	None	None	Falsified
11	200	USA	USA	English	Genuine

Price

The price of genuine 100 mg Diflucan® tablets was 2,634 ± 149 yen/tablet, while the price of the falsified Diflucan® tablet was 1,316 yen/tablet. The 200 mg Diflucan® tablet cost 2,733 yen/tablet. Comparing the prices of 100 mg Diflucan® tablets, the price of the falsified tablet was lower than that of the cheapest genuine tablet.

Visual inspection

We only tested the 100 mg Diflucan® tablets (not the 200 mg tablet) because a standard 100 mg Diflucan® tablet was obtained from the manufacturer for comparison. Notably, there was a spelling error on the English label of the falsified bottle ("DOSAGF" instead of "DOSAGE"). In addition, the falsified sample arrived with a past-due expiration date on the bottle. Pfizer reported to us that this was an old bottle type that had been discontinued more than 10 years before.

The average dimensions of standard 100 mg Diflucan® tablets, genuine 100 mg Diflucan® tablets, and falsified tablets were 6.90, 6.90, and 7.20 mm in width; 10.03, 10.04, and 10.43 mm in length; and 3.59, 3.57, and 5.92 mm in thickness, respectively. Standard and genuine 100 mg Diflucan® tablets were similar in size, while the falsified tablets were larger and thicker; however, as there was only one falsified sample, statistical analysis could not be performed.

The average ΔE^*ab between standard and genuine 100 mg tablets was 1.50–2.80, whereas the ΔE^*ab between standard and falsified tablets was 17.26. Color is generally regarded to be different when $\Delta E^*ab > 13$, so the falsified tablet was confirmed to differ in color from the standard tablet.[33]

Quality evaluation

Of the 11 samples, 10 passed the quantity and content uniformity test. Fluconazole was not detected in Sample No.10. In all other samples, the average content of ten tablets per sample ranged from 99.6% to 103.7%, thus passing the quantity evaluation. Acceptance value ranged from 2.1% to 4.6%; therefore, samples passed the content uniformity test.[32] In this study, the dissolution rates of all three tablets for each sample, except Sample No.10, were 89.0%–100.4%.

The falsified tablet (Sample No.10) differed from standard tablets in terms of its retention time and ultraviolet spectrum, which were similar to those of sildenafil citrate; moreover, the maximum absorption wavelength was almost identical between the falsified tablet and sildenafil citrate (Figures 1 and 2). The peak of a mixture of sildenafil citrate reference standard and Sample No.10 completely overlapped and was not split, such that only a single peak was detected. These results indicate that Sample No.10 contained sildenafil citrate instead of fluconazole.

Spectroscopy

The near-infrared spectra did not differ between standard and genuine tablets, whereas there were differences in the spectra of standard and falsified tablets around 1600–1700 and 2200–2400 nm (Figure 3).

No differences were observed between the Raman spectra of standard and genuine tablets by two analyzers (Figures 4 and 5). No peak could be confirmed for the falsified tablet by a triple grating spectrometer, whereas a portable scattering analyzer yielded a spectra of the falsified tablet that clearly differed from that of the standard tablet.

Discussion

We assessed the quality of Diflucan® tablets purchased online, which are advertised by some Japanese websites as "female Viagra®." Our findings clearly show that at least one falsified Diflucan® tablet is distributed through online

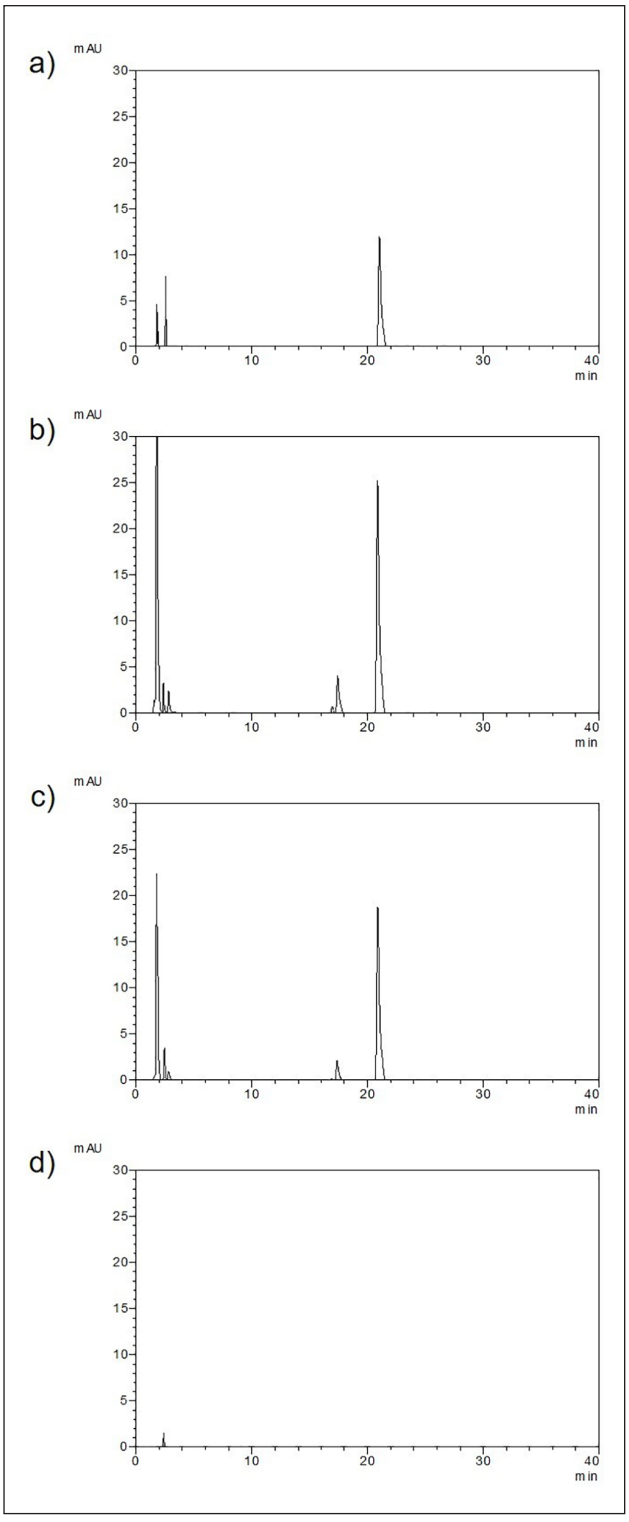

Figure 1. The chromatograms obtained from HPLC analysis. The detection wavelength was 293 nm. (a) Reference standard of sildenafil citrate, (b) Sample No.10, (c) mixture of sildenafil citrate reference standard and Sample No.10 (1:1, v/v), and (d) reference standard of fluconazole.

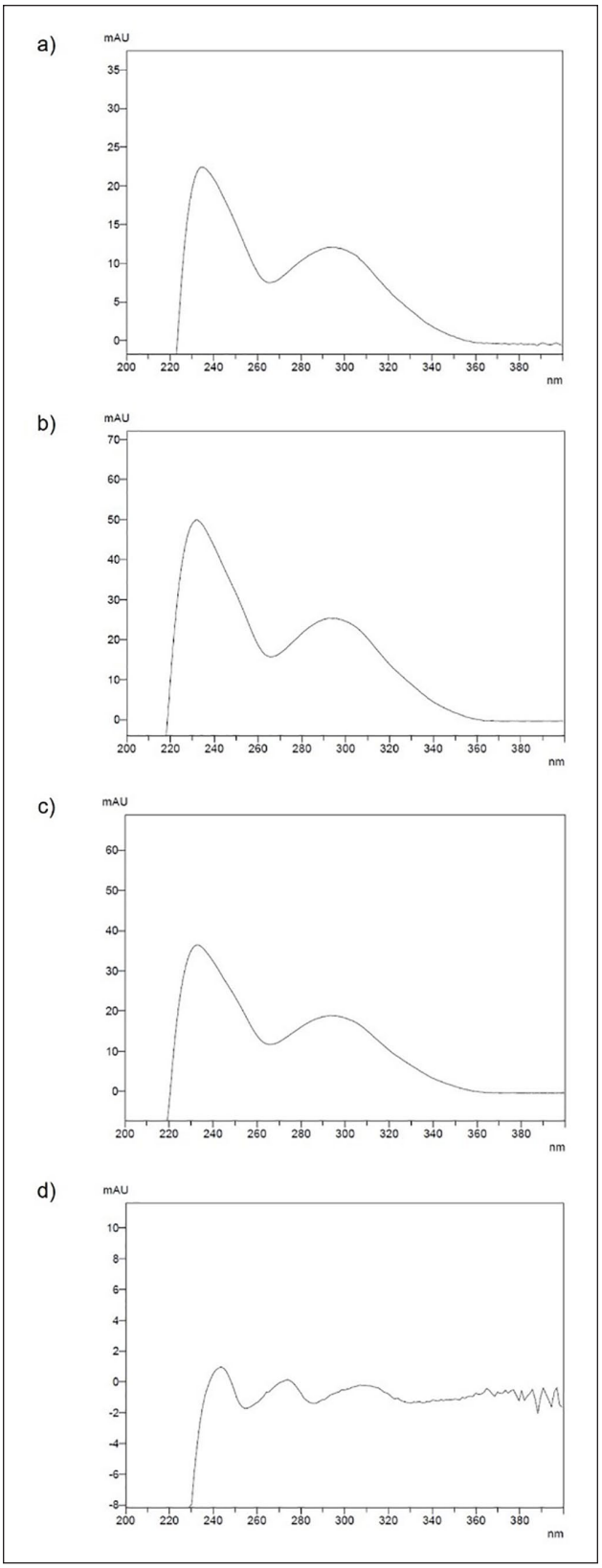

Figure 2. *(Continued)*

Figure 2. The ultraviolet spectrum of the peak around 21 min obtained from HPLC analysis. (a) Reference standard of sildenafil citrate, (b) Sample No.10, (c) mixture of sildenafil citrate reference standard and Sample No. 10 (1:1, v/v), and (d) reference standard of fluconazole.

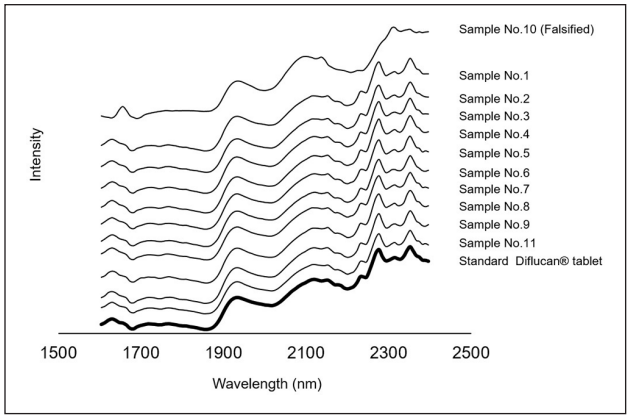

Figure 3. Near-infrared spectra of Diflucan® tablets ($n = 12$).

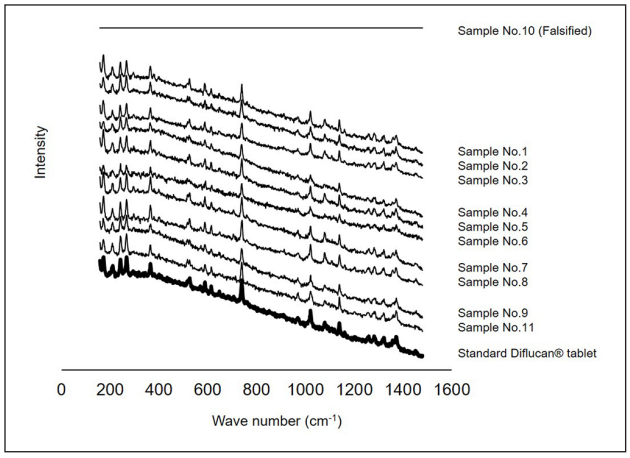

Figure 4. Raman spectra of Diflucan® tablets obtained using a triple grating spectrometer ($n = 12$).

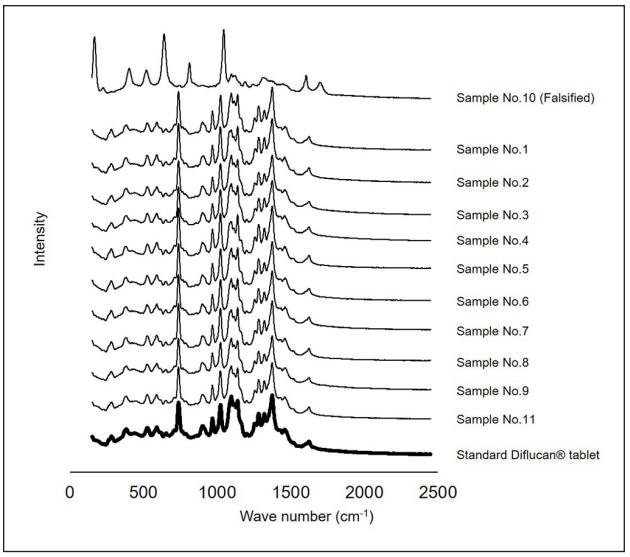

Figure 5. Raman spectra of Diflucan® tablets obtained using a portable scattering analyzer ($n = 12$).

sources, indicating the danger of ordering Diflucan® tablets online (Table 1).

Of the 11 sites, 7 mentioned an effect of fluconazole on sexual function that has not been medically approved, although there was no mention of sexual effect on any of the products we actually received from these sites; thus, we considered it difficult to judge only from the description on the site whether the product is a falsified medicine. Because the one falsified tablet obtained in this study was cheaper than all the genuine tablets, it might be a risk to personally import medicines just because the price is low. The falsified Diflucan® tablet had an incorrect bottle label and differed in tablet size and color from the standard Diflucan® tablet, although consumers may not know the visual characteristics of the standard product. Because the falsified Diflucan® tablet did not contain fluconazole, the anticipated antifungal therapeutic effect would not be obtained. Furthermore, the presence of sildenafil citrate may lead to cardiovascular effects in susceptible populations (Figures 1 and 2).[34]

Using NIR and Raman scattering spectroscopy for nondestructive analysis of the tablets, we were able to identify one falsified sample (Figures 3–5). To prevent the inflow of falsified medicines, spectroscopic analysis by portable analyzers could be used as a rapid and reliable method of detecting falsified medicines at the customs checkpoint. Raman scattering spectroscopy shows a sharp peak suitable for visual observation, but the spectra cannot be obtained for products with strong fluorescence emission (Figure 4). As shown in Figure 5, the falsified tablet exhibited differences in several peaks, so selecting an instrument with a proper wavelength is important. In this study, we considered both NIR and Raman scattering spectroscopy to be useful in identifying the one falsified Diflucan® tablet. Robust systems for detecting falsified medicines will contribute to ensuring the quality of distributed therapeutics and minimizing the damage caused by falsified medicines.

Potential confounding factors for this study include a limited sampling period and sociocultural element, as samples were purchased from only Japanese sites. In this study, only one falsified Diflucan® tablet was obtained, so it was difficult to determine boundaries between genuine and falsified Diflucan® tablets. However, the falsified Diflucan® tablet obtained in this study exhibited characteristics differing from genuine tablets, such as larger size and different color, so it might be possible to visually identify falsified Diflucan® tablets. In addition, Diflucan® tablets advertised as "female Viagra®" on the purchasing

site did not exhibit source information, such as the shipping country. If there are some suspicious claims on the site or the appearance of the product varies, it should be suspected to be falsified. Based on the results of this study, at least one falsified Diflucan® tablet is distributed online, indicating the risk of obtaining medicines by personal import.

As another limitation of the study, we could not perform an accurate dissolution test with six tablets per sample because an insufficient number of tablets was available for testing by all the various identification methods.[32] False labeling, insufficient active pharmaceutical ingredient, and poor dissolution must all be considered during analysis. Although all 100 mg Diflucan® tablets found on Japanese Internet sites were purchased and their authenticity was confirmed, the number of samples was small; thus, further study involving an increased number of samples is necessary. In that case, the effectiveness of the identification methods described herein will be evaluated by confirming the results of authenticity judgments with the manufacturer. The falsified sample was the only one that did not contain fluconazole, but this is one of only a few reports providing details about falsified Diflucan® tablets. Ethics approval was not required for this research because it did not involve research on humans or animals.

Conclusion

Fluconazole was sometimes advertised online as having an effect on female sexual function. One falsified Diflucan® tablet, which contained sildenafil citrate, was confirmed to be available in the online market. This finding is important because sildenafil citrate might cause unexpected health hazards. Thus, continued measures against falsified medicines are necessary and will support their elimination.

Acknowledgements

The authenticity investigation was supported by Pfizer Japan, Inc. (Tokyo, Japan). Spectrocolorimetry was supported by Shachihata Inc. (Aichi, Japan). Near-infrared analysis was supported by ST Japan Inc. (Tokyo, Japan). Raman triple-grating scattering analysis was conducted at the Japan Advanced Institute of Science and Technology, and was supported by the Nanotechnology Platform Program (Molecule and Material Synthesis) of the Ministry of Education, Culture, Sports, Science and Technology, Japan. Portable Raman scattering analysis was supported by Higuchi Inc. (Tokyo, Japan).

Author contributions

Conceptualization, Project administration and Resources: Naoko Yoshida, Kazuko Kimura; Data curation, Validation and Visualization: Tomoko Sanada, Myu Ohnishi; Formal analysis: Tomoko Sanada, Myu Ohnishi, Naoko Yoshida, Hirohito Tsuboi; Funding acquisition and Supervision: Kazuko Kimura; Investigation and Methodology: Tomoko Sanada, Myu Ohnishi, Naoko Yoshida, Kazuko Kimura; Writing—original draft preparation: Tomoko Sanada; Writing—review and editing: Tomoko Sanada, Myu Ohnishi, Naoko Yoshida, Kazuko Kimura, Hirohito Tsuboi.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Health and Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare, Japan [H26-地球規模A-指定-003].

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Supplemental material

Supplemental material for this article is available online.

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