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Availability and Chemical Assessment of Dextromethorphan and Diphenhydramine Products Purchased through Personal Import Websites

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In recent years, overdoses related to over-the-counter medicines have become a serious social problem in Japan. As some medicines have been designated as abuse-prone and sales regulations have been strengthened, there is concern that these medicines might be obtained via personal importation. This study focused on dextromethorphan and diphenhydramine, which have been reported to be misused despite not being designated as abuse-prone medicines in Japan. This study investigated public health concerns related to their personal importation to provide evidence to prevent overdoses. Between July 31 and September 8, 2023, products containing these substances were purchased from personal import agency websites. Website information at the time of purchase was reviewed, and the products were examined for appearance, authenticity, and active pharmaceutical ingredient content. In total, 3 dextromethorphan products and 21 diphenhydramine products, all of which were unapproved medicines in Japan, were obtained. Although some products appeared to be prescription-only based on labeling, no prescriptions or identity verification was required, and quantities equivalent to a 1–2-month supply were easily obtained. Most products were also cheaper per tablet than domestically marketed medicines. Appearance inspections revealed inappropriate labeling, damaged tablets, and contaminated packaging. Manufacturers did not respond to authenticity inquiries. The active pharmaceutical ingredient content was approximately 100% of the labeled amount in all samples. Although no clear counterfeit items were identified, substandard-quality medicines were detected. These findings indicate that personal importation should be considered when developing measures to prevent inappropriate over-the-counter medicine use and related health risks.

Key words over-the-counter medicine, abuse, personal import, Internet

INTRODUCTION

Abuse of over-the-counter (OTC) medicines by young people has become a social problem in Japan.[1-2] The number of patients addicted to OTC medicines increased 6-fold from 2012 to 2020.[3] At the same time, reports of health harms caused by the misuse of OTC medicines have also increased.[4-12] To avoid these issues, pharmacies and drugstores are taking measures such as limiting the number of OTC medicines that can be purchased at one time. There is a serious concern that restricting medicine purchase through proper distribution channels could result in increased purchase through improper distribution channels. A typical improper distribution channel is the personal import of medicines via the Internet. Medicine import is prohibited in principle, but if the medicines are intended for personal use, a 1-month supply of prescription medicines or 2-month supply of OTC medicines can be imported without an application for import permission.[13] In addition to six types of OTC medicines that are already subject to stricter regulations,[14] diphenhydramine and dextromethorphan are being increasing purchased purchasing for the purpose of abuse.[2] Cases of acute poisoning and death attributable to confusion, rhabdomyolysis, and serotonin syndrome associated with diphenhydramine overdose have been reported in Japan.[15-17] In addition, there are reports of acute poisoning and death among young people who consumed large amounts of dextromethorphan.[18-20] To investigate the actual situation, quality, and authenticity of these medicines distributed globally via the Internet, we imported diphenhydramine and dextromethorphan preparations distributed via the Internet to assess their quality and investigate their authenticity.

MATERIALS AND METHODS

Sample Collection We used Google Japan to identify websites selling dextromethorphan and diphenhydramine

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using the search terms "dextromethorphan personal import" and "diphenhydramine personal import" in Japanese. All personal import agency websites identified through Google Japan searches that offered dextromethorphan tablets or diphenhydramine tablets to consumers in Japan and allowed delivery to Japan were included. All products available for purchase during the survey period were included in the analysis.

Visual Observation We examined the purchased products to confirm basic information, the language used, and the presence or absence of a package insert for each sample. Additionally, the packaging form, inappropriate descriptions on the outer packaging, and the presence of stains or scratches on the tablets were recorded. Details regarding packaging and inserts were stored as scanned data, and container packaging details were recorded as photographs.

Purchase Price We calculated the purchase price, excluding shipping and importation fees, per dextromethorphan or diphenhydramine tablet using information available on the Internet.

According to consumer purchasing data provided by True Data Inc., Drewell 12 tablets accounted for the largest market share (42.6%) among OTC sleep-improving medicines in 2023.[21] The price of diphenhydramine tablets was compared with the manufacturer's suggested retail price (tax included) of the OTC medicine "Drewell 12 tablets."

According to True Data Inc. consumer purchasing data, Medicon Cough Suppressant Tablets Pro 20 tablets was the most popular dextromethorphan-containing antitussive medicine in 2023, with a market share of 5.8%.[22] The price of dextromethorphan tablets was compared with the manufacturer's suggested retail price (tax included) of the OTC medicine "Medicon cough suppressant tablets Pro 20 tablets."

Authenticity Investigation On January 31, 2024, we sent email communications to six manufacturers and distributors (three each for dextromethorphan and diphenhydramine). On February 22, 2024, we sent sample appearance photographs and questionnaires via Express Mail Service (EMS).

The questionnaire included questions based on the results of the visual inspection, covering the authenticity of the product name, manufacturing date, expiration date, and information printed on the outer packaging, as well as whether the manufacturing company holds a license for manufacturing and sales in its country of origin, whether the product is approved, and whether measures against counterfeits have been implemented.

Details Provided on Websites We observed and documented whether websites provided the following information required under the Specified Commercial Transactions Act[23] for personal imports into Japan: name of the representative or responsible person; business name, address, and telephone number; product price; shipping costs; payment date and time; product delivery date and time; payment method; and return policy.

Additionally, we recorded whether each website provided the following information related to the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices (Japanese law translation):[24] statement advising consultation with a physician or pharmacist; personal import instructions; purchase quantity limit instructions; medication instructions; and medical consultation contact information.

Materials Acetonitrile, ammonium nitrate, and phosphoric acid were purchased from Fujifilm Wako Pure Chemical Corporation (Kyoto, Japan). Dioctyl sodium sulfosuccinate was obtained from Tokyo Kasei Sales Co., Ltd. (Tokyo, Japan). Glacial acetic acid and potassium dihydrogen phosphate were procured from Nacalai Tesque Co., Ltd. (Kyoto, Japan). Acetonitrile, acetic acid, and phosphoric acid were of HPLC grade, whereas dioctyl sodium sulfosuccinate, potassium dihydrogen phosphate, and ammonium nitrate were of reagent grade. The standard reference material for dextromethorphan hydrobromide hydrate was the USP (Rockville, MD, USA) Reference Standard. The standard reference material for diphenhydramine hydrochloride was pharmaceutical secondary standard, certified reference material (Sigma-Aldrich, St. Louis, MO, USA). To compare the average content rates of personally imported samples with HPLC, commercially available Japanese products were used. Medicon Cough Suppressant Tablets Pro (Shionogi Healthcare Co., Ltd., Osaka, Japan) was used as the reference product for dextromethorphan preparations. Drewell (SS Pharmaceutical Co., Ltd., Tokyo, Japan) was used as the reference product for diphenhydramine preparations.

Qualitative and Quantitative Analysis of Tablets Qualitative and quantitative analyses of active ingredients in personally imported dextromethorphan and diphenhydramine tablets were performed using high-performance liquid chromatography (HPLC). The HPLC system consisted of a LaChrom Elite Organizer, Pump L-2130, Autosampler L-2200, Column Oven L-2300, and a Primaide 1430 diode array detector (Hitachi High-Technologies Corporation, Tokyo, Japan).

For dextromethorphan analysis, separation was achieved using a Mightysil RP-18 GP column (150 × 4.6 mm, 5 μm; Kanto Chemical Co., Inc., Tokyo, Japan). The detection wavelength was 280 nm, the flow rate was 1.0 mL/min, and the column temperature was maintained at 35°C. The injection volume was 10 μL, and the run time was 20 min. The mobile phase consisted of acetonitrile and water (65:35, v/v) containing 0.007 M dioctyl sodium sulfosuccinate and 0.007 M ammonium nitrate, with the pH adjusted to 3.4 using glacial acetic acid.

Diphenhydramine analysis was conducted using the same column at a detection wavelength of 220 nm, flow rate of 1.0 mL/min, column temperature of 35°C, injection volume of 20 μL, and run time of 16 min. The mobile phase consisted of acetonitrile and 0.04 M potassium dihydrogen phosphate buffer (pH 3.0) mixed at 30:70 (v/v).

For each product, three tablets were analyzed individually. Active pharmaceutical ingredient (API) content was expressed as a percentage of the labeled amount and was calculated as follows:

$$\text{API content (\%)} = A/B \times 100$$

where A is the amount of dextromethorphan hydrobromide or diphenhydramine hydrochloride determined for each tablet, and B is the labeled amount declared on the product package. Identification was confirmed by comparing retention times with those of the corresponding reference standards.

RESULTS AND DISCUSSION

Sample Collection Google searches were conducted on April 21, 2023, to identify websites offering products containing dextromethorphan or diphenhydramine. All person-

al import agency websites identified through Google Japan were screened for dextromethorphan- and diphenhydramine-containing products. Products that were out of stock, discontinued, restricted for purchase, or required additional import verification procedures were excluded. The numbers of identified websites and products, purchased products, and products included in the analysis are shown in Fig. 1.

Orders for the identified products were placed between August 1 and August 3, 2023, and all products were received by September 8, 2023. We obtained three samples of 5-, 15-, and 20-mg dextromethorphan tablets from three websites and 21 samples of 25-mg diphenhydramine tablets via the Internet.

All products that could be successfully ordered from the identified online vendors during the survey period were collected; consequently, three dextromethorphan tablet products and 21 diphenhydramine tablet products were included in this study. Tables 1 and 2 provide specific information for the collected samples. Based on the labeled dosage instructions provided on each product, the purchased quantities corresponded to approximately 1–2 months or more of use for both dextromethorphan and diphenhydramine products. There was no description on any of the identified purchasing websites specifying whether the medicines were OTC products. However, no prescription was required by any of the websites during the purchasing process. There are risks that medicines distributed via the Internet can contain substandard, falsified, unapproved, and unlicensed medicines.[25-29] If consumers use falsified or substandard products, then they may not achieve the desired results, or they could experience unexpected adverse events.

Visual Observation

Dextromethorphan The purchased dextromethorphan products comprised three samples from three brands (A, B, and C) in three different packaging formats. The 15-mg product of brand A was packaged in a bottle. Although the ordering website displayed an image of a light blue bottle, the received product consisted of a white bottle with Japanese labels affixed and a traditional Chinese instruction leaflet secured with a rubber band. Discrepancies between the product images displayed on the ordering website and the actual packaging received made it difficult for consumers to confirm whether the ordered product was correctly delivered, raising concerns regarding traceability and authenticity in Internet-based medicine distribution. Inside the bottle, white tablets were enclosed within a transparent zipper pouch. One damaged tablet was found in the pouch, although no visible fragments were present, and powder residue was observed inside the packaging, suggesting possible abrasion of the tablet surface. Tablet abrasion can lead to a reduction in the API content and promote internal degradation of the tablet. The 20-mg product of brand B was packaged in a box, and no apparent signs of tampering were observed. By contrast, the 5-mg product of brand C was wrapped in SP film, and black stains were observed on the primary packaging. These findings indicate that quality control during manufacturing, packaging, or distribution might not have been consistently and adequately implemented. All packaging bore the label "Dosage: As directed by a physician," suggesting all three purchased samples were prescription medications. Excluding product A, which came with foreign-language instruction, none of the other samples include instructions or usage guides.

Diphenhydramine In total, 21 diphenhydramine samples were obtained from three brands (D, E, and F) in three different packaging formats. Brand D accounted for the largest number of samples (n = 10), all of which were packaged in boxes, whereas samples for brands E (n = 7) and brand F (n = 4) were packaged in bottles. Although brands E and F were marketed as distinct products, the tablets exhibited highly similar shapes, colors, and embossed markings, suggesting similarities in manufacturing despite differences in product labeling. All samples of brands E and F listed the additive

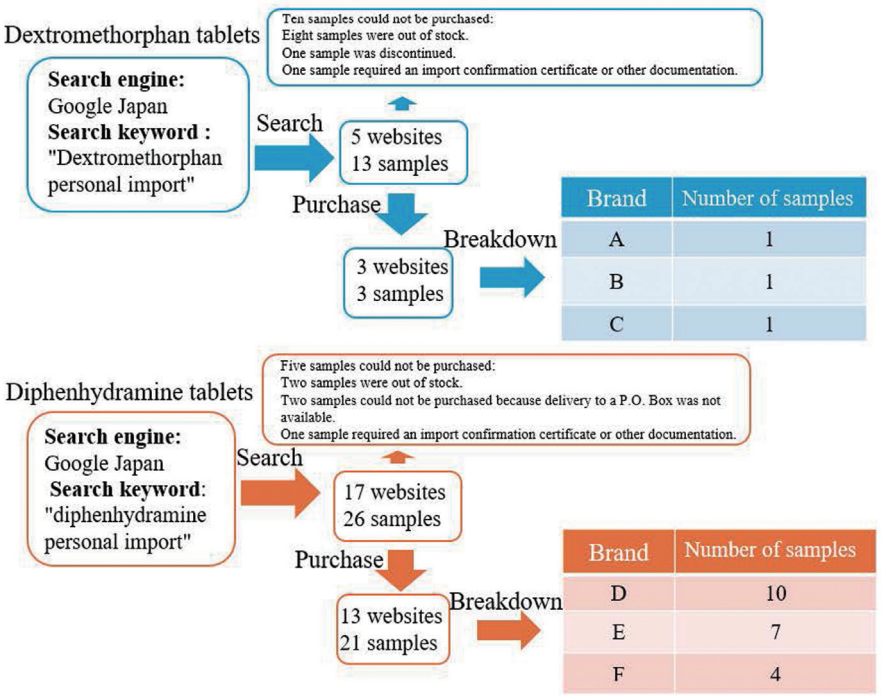


Fig. 1. Flowchart of Sample Collection for Dextromethorphan and Diphenhydramine Tablets

Table 1. List of Collected Dextromethorphan Samples

Sample No.	Brand	Dose (mg)	Number of pills	Outer packaging	Language	Labeled manufacturing and/or distributing country	Shipping country	Package insert and language	Authenticity	Estimated Drug Classification (estimated)
1	A	15	250	Bottle	Japanese	Taiwan	Taiwan	Yes/ Traditional Chinese	Unknown	Prescription
2	B	20	100	Box	English	India	Hong Kong	None	Unknown	Prescription
3	C	5	60	Sheet	English	India	India	None	Unknown	Prescription

Table 2. List of Collected Diphenhydramine Samples

Sample No.	Brand	Dose (mg)	Number of pills	Outer packaging	Language	Labeled manufacturing and/or distributing country	Shipping country	Package insert and language	Authenticity	Estimated Drug Classification (estimated)
1-10	D	25	144	Box	English	No record	USA	None	Unknown	OTC
11-17	E	25	100	Bottle	English	No record	Hong Kong	None	Unknown	OTC
18-21	F	25	600	Bottle	English	USA	Hong Kong	None	Unknown	OTC

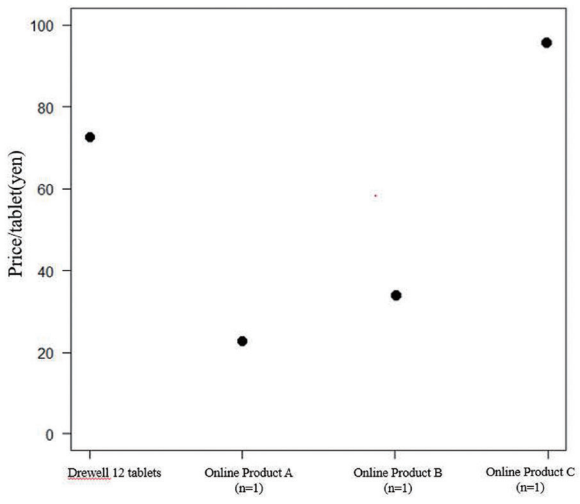


Fig. 2. Comparison of the Manufacturer's Suggested Retail Price for Diphenhydramine Tablets (OTC Medicine "Drewell," Which Is Sold in a Pack of 12 Tablets) in Japan and the Price of Tablets Obtained by Personal Import Via the Internet.

n indicates the number of independent samples.

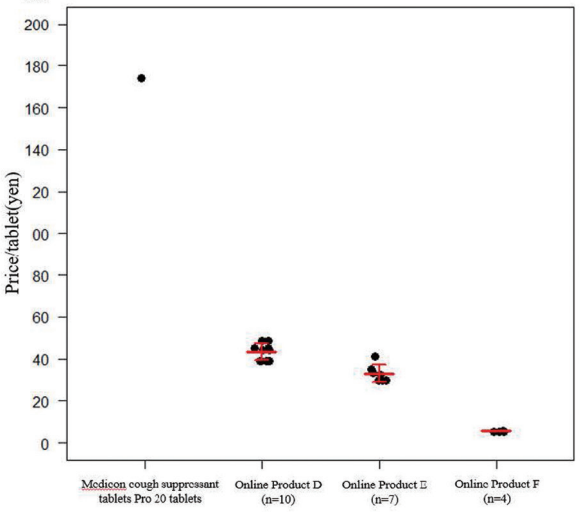


Fig. 3. Comparison of the Manufacturer's Suggested Retail Price for Dextromethorphan Tablets (OTC Medicine "Medicon Cough Suppressant Tablets Pro," Which Is Sold in a Pack of 20 Tablets) in Japan and the Price of Tablets Obtained by Personal Import via the Internet.

Data are shown as mean (red dots) ± SD (error bars). n indicates the number of independent samples.

"D&C Red No. 27 Aluminum Lake." In Japan, this colorant (Red No. 218) is permitted only for use in topical medicines, and it is not approved for use in oral medicines under the Ministry of Health, Labour and Welfare Ordinance No. 30. Although no reports describing adverse effects following oral intake were identified, the safety of ingesting this colorant has not been established; therefore, potential safety concerns remain. None of the 21 diphenhydramine samples bore the statement "Dosage: As directed by a physician;" instead, the packaging clearly specified usage and dosage instructions, indicating the product was an OTC medicine. Upon reviewing documentation, none of the samples included accompanying instructions or usage guides.

Consumers obtaining medicines via personal importation without professional guidance might rely on package inserts for appropriate use. However, many products lacked inserts or failed to provide information in Japanese, which could impede correct administration and increase the risk of inappropriate use.

Purchase Price A comparison of the manufacturer's suggested retail prices for diphenhydramine tablets in Japan and those purchased online is shown in Fig. 2. The manufacturer's suggested retail price for diphenhydramine (Drewell 12 tablets) in Japan was 174.2 yen/tablet, and the prices of all purchased samples were lower than the manufacturer's suggested retail price.

A comparison of the manufacturer's suggested retail prices for dextromethorphan tablets in Japan and those purchased online is shown in Fig. 3. The manufacturer's suggested retail price for OTC dextromethorphan (Medicon Cough Suppressant Tablets Pro, 20 tablets) in Japan was 72.6 yen/tablet. The prices of the samples purchased were lower than the manufacturer's suggested retail price, excluding one sample.

These lower prices could be one of the motivations for consumers to use personal imports to purchase these two medicines.

Authenticity We sent the questionnaire regarding the authenticity of the acquired products and photographs of their appearance to the manufacturers and distributors via email and EMS but received no response from either party. This lack of response indicates that medicines obtained through personal importation exhibit significant deficiencies in source verification and information transparency. As relevant information cannot be obtained, their safety cannot be adequately assessed; therefore, the possibility that such products pose potential risks to users' health cannot be dismissed.

Evaluation of Website Details All dextromethorphan and diphenhydramine samples were purchased from identified personal import agency websites. Dextromethorphan products were obtained from three websites, whereas diphenhydramine products were obtained from 13 websites.

Among the dextromethorphan websites, all described the products as cough suppressants, and one website included customer reviews referring to cough relief. Among the diphenhydramine websites, 12 of 13 advertised the products as being used to relieve allergy symptoms or improve sleep, and several included customer reviews referring to such uses.

Tables 3 and 4 summarize information provided on the websites in relation to the Specified Commercial Transactions Law and the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, with detailed website-level data presented in Supplementary Tables 1–4. Basic commercial information was provided on all diphenhydramine websites and on most dextromethorphan websites. All websites stated that the products were intended for personal importation, and quantity limits were indicated.

Product names and identifiable product images were displayed on all websites. Concerning pharmaceutical-related information, the availability of information on dosage, indications, and adverse effects varied among the websites, with such information more frequently provided for diphenhydramine products than for dextromethorphan products.

Qualitative and Quantitative Analysis of Tablets Qualitative and quantitative analyses of the APIs in the obtained dextromethorphan and diphenhydramine products were performed using HPLC, and the results are presented in Tables 5 and 6.

For the dextromethorphan products, namely Fudecough 15 mg (a generic formulation of Medicon), Dextromethorphan Tablet 20 mg DMR-20, and Dextromethorphan Hydrobromide Lozenges 5 mg Alex®, the API contents relative to the labeled amount were 101.5% ± 2.0%, 99.7% ± 0.8%, and 102.2% ± 0.3%, respectively. For the diphenhydramine products, the API content relative to the labeled amount ranged from 99.0% to 101.9%.

Although both qualitative and quantitative HPLC analyses identified no significant deviations in API content and detected no impurity peaks, even when personally imported products are authentic, the quality control standards of overseas manufacturers might not be equivalent to those required in Japan. Consequently, the potential for insufficient quality control or production under unhygienic conditions cannot be dismissed. Therefore, the safety and quality of medicines obtained through personal importation cannot be regarded as assured.

The Risk of Abuse Associated with Personal Medicine Import Our prior research provided information on the risk of personal import of medicines and warned people to avoid casually importing these products.[25-29] We are extremely concerned that if legal distribution channels are regulated strictly, then more people could be motivated to access illegally distributed medicines, such as those obtained by personal import. To prevent improper medicine use while strengthening the rules on purchase quantity limits, it is also important to seek measures to prevent OTC medicines with abuse potential from being obtained by consumers through personal import via the Internet. Careful consideration is required to strengthen regulations on the sale of OTC medicines to prevent further health hazards. This article provides a warning about the potential increase in personal imports of medicines for abuse.

Limitations This study has several limitations. First, only dextromethorphan and diphenhydramine were examined through online purchases. Furthermore, the analysis focused exclusively on products obtained via personal importation. Therefore, our findings do not reflect the quality of all medications available online or the online purchasing patterns of other potentially misused drugs.

Because we collected all products available on Japanese websites during the study period, the results can be considered representative of the situation at that time under these conditions. However, this scope is inherently limited to products available on Japanese websites during the study period and does not necessarily reflect products currently in circulation. In addition, although we attempted to purchase all products available during the study period, we may not have identified all dextromethorphan and diphenhydramine products available on Japanese merchant sites.

Due to variations in manufacturers, production volumes, and distribution quantities, the findings of this study are difficult to generalize to other medications. Expanding the analysis to include other medicines that are susceptible to misuse may provide more comprehensive information and additional insights.

In addition, this study evaluated the active ingredient content and chromatographic profiles of the purchased products; however, dissolution characteristics and bioequivalence with approved products were not assessed. Therefore, the therapeutic equivalence of the purchased products to officially marketed products remains unclear.

Finally, we did not obtain feedback from manufacturers regarding product authenticity; therefore, the authenticity of the samples collected could not be verified. These findings highlight the need for active collaboration between manufacturers and regulatory authorities to improve the quality of medications sold online.

Conclusion In this study, products containing dextromethorphan and diphenhydramine obtained through personal importation via the Internet were investigated using a test purchase approach, and their accessibility, information provision, and product quality were comprehensively evaluated. The results demonstrated that these medicines could be read-

Table 3. Display Status of Items Required under the Act on Specified Commercial Transactions on the Surveyed Purchase Website
Table 3-1. Websites Selling Dextromethorphan according to Requirements of the Specified Commercial Transactions Law

Required detail	Number of websites (%)
Name of a representative or responsible person	2 (67.0)
Name of business	3 (100.0)
Address of business	2 (67.0)
Telephone number	2 (67.0)
Product price	3 (100.0)
Shipping fee	3 (100.0)
Payment date and time	3 (100.0)
Product delivery date and time	3 (100.0)
Payment method	3 (100.0)
Conditions for return	3 (100.0)

The number of websites analyzed was 3 (n = 3).

Table 3-2. Websites Selling Diphenhydramine according to Requirements of the Specified Commercial Transactions Law

Required detail	Number of websites (%)
Name of a representative or responsible person	11 (84.6)
Name of business	13 (100.0)
Address of business	13 (100.0)
Telephone number	11 (84.6)
Product price	13 (100.0)
Shipping fee	13 (100.0)
Payment date and time	13 (100.0)
Product delivery date and time	13 (100.0)
Payment method	13 (100.0)
Conditions for return	13 (100.0)

The number of websites analyzed was 13 (n = 13).

Table 4. Status of Descriptions Related to the Pharmaceuticals and Medical Devices Act and Health-Related Items on the Surveyed Purchase Websites
Table 4-1. Websites Selling Dextromethorphan according to the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

Required detail	Number of websites (%)
A statement recommending consultation with a doctor or pharmacist	3 (100.0)
A description of personal importation	3 (100.0)
A statement on the purchase quantity limit	3 (100.0)
Description of unapproved medicines or ethical medicines	
The name of the product	3 (100.0)
A photograph of the product	3 (100.0)
Dose of the active ingredient	0 (0.0)
Description of the active pharmaceutical ingredient	2 (66.7)
Description of potential side effects	1 (33.3)

The number of websites analyzed was 3 (n = 3).

Table 4-2. Websites Selling Diphenhydramine according to the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

Required detail	Number of websites (%)
A statement recommending consultation with a doctor or pharmacist	10 (78.0)
A description of personal importation	13 (100.0)
A statement on the purchase quantity limit	13 (100.0)
Description of unapproved medicines or ethical medicines	
The name of the product	13 (100.0)
A photograph of the product	13 (100.0)
Dose of the active ingredient	10 (76.9)
Description of the active pharmaceutical ingredient	12 (92.3)
Description of potential side effects	9 (69.2)

The number of websites analyzed was 13 (n = 13).

Table 5. Assay Results of Dextromethorphan Tablets: API Content (%)

Sample No.	Brand	Tablet 1	Tablet 2	Tablet 3	Mean ± SD
1	A	103.1	98.7	102.8	101.5 ± 2.0
2	B	100.8	99.1	99.1	99.7 ± 0.8
3	C	102.3	102.5	101.8	102.2 ± 0.3

Data are presented as mean ± SD relative to the labeled amount.
The number of tablets analyzed per sample was 3 (n = 3).
API contents are presented for descriptive purposes only; no pharmacopoeial acceptance criteria were applied.

Table 6. Assay results of diphenhydramine tablets: API content (%)

Sample No.	Brand	Tablet 1	Tablet 2	Tablet 3	Mean ± SD
1	D	97.9	105.5	100.5	101.3 ± 3.2
2	D	95.4	100.7	101.0	99.0 ± 2.6
3	D	102.0	98.9	100.8	100.6 ± 1.3
4	D	97.3	99.6	100.8	99.2 ± 1.5
5	D	103.4	101.3	100.5	101.7 ± 1.2
6	D	98.7	102.9	98.8	100.1 ± 1.9
7	D	101.1	101.4	99.0	100.5 ± 1.0
8	D	100.8	102.5	98.9	100.7 ± 1.5
9	D	100.4	99.0	100.8	100.1 ± 0.7
10	D	99.0	99.8	99.0	99.3 ± 0.4
11	E	99.2	97.7	100.6	99.2 ± 1.2
12	E	101.5	100.3	102.4	101.4 ± 0.9
13	E	98.5	96.8	101.7	99.0 ± 2.0
14	E	103.4	98.8	102.7	101.6 ± 2.0
15	E	103.4	98.3	100.4	100.7 ± 2.1
16	E	103.4	100.3	102.2	101.9 ± 1.3
17	E	103.1	103.1	99.5	101.9 ± 1.7
18	F	97.9	100.5	98.7	99.1 ± 1.1
19	F	99.1	100.4	99.9	99.8 ± 0.5
20	F	96.4	101.2	99.5	99.0 ± 2.0
21	F	101.3	93.9	103.1	99.4 ± 4.0

Data are presented as mean ± SD relative to the labeled amount.
The number of tablets analyzed per sample was 3 (n = 3).
API contents are presented for descriptive purposes only; no pharmacopoeial acceptance criteria were applied.

ily obtained through personal importation, and some products exhibited problems related to labeling and quality management. In addition, their distribution was not fully subject to the domestic regulatory framework governing authorized pharmaceutical sales. Although experimental analyses did not reveal significant deviations in active ingredient content, deficiencies in source traceability and safety assurance remain for personally imported medicines.

Although diphenhydramine and dextromethorphan tablets have since been included in the "Designation of abuse-prevention pharmaceuticals"[28] issued by the Ministry of Health, Labour and Welfare of Japan, they had not yet been designated as such at the time of our test purchase investigation. Furthermore, our survey results illustrated that 1-2-month supplies of diphenhydramine and dextromethorphan tablets, which are difficult to purchase in Japan, could be easily obtained online via personal importation at lower prices. This situation might allow Japanese individuals to import medicines more readily, thereby increasing the risk of accidents related to improper use and potential health harms.

Alongside the strengthening of domestic regulations on pharmaceutical sales, regulatory measures targeting the personal importation of medicines should be further advanced. Medicines obtained through personal importation are used without professional guidance and are not covered by the adverse drug reaction relief system. Therefore, it is necessary to provide appropriate information and warnings to prevent consumers from casually importing medicines for personal use. In addition, enhanced monitoring and guidance of personal import intermediaries and shipping operators are considered essential to prevent inappropriate sales practices. Overall, the present study might provide a reference for future surveillance and regulatory assessments.

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Conflict of interest The authors declare no conflict of interest.

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