Am. J. Trop. Med. Hyg., 97(3), 2017, pp. 684–689
doi:10.4269/ajtmh.16-0971

Classification and Visualization of Physical and Chemical Properties of Falsified Medicines with Handheld Raman Spectroscopy and X-Ray Computed Tomography

Tomoko Kakio,[1]* Naoko Yoshida,[2] Susan Macha,[3] Kazunobu Moriguchi,[1] Takashi Hiroshima,[1] Yukihiro Ikeda,[1] Hirohito Tsuboi,[2] and Kazuko Kimura[2]

[1]*Analytical Development, Pharmaceutical Sciences, Takeda Pharmaceutical Company, Ltd., Osaka, Japan;* [2]*Drug Management and Policy, Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan;* [3]*Global Product Protection, Takeda Pharmaceuticals U.S.A., Inc., Deerfield, Illinois*

Abstract. Analytical methods for the detection of substandard and falsified medical products (SFs) are important for public health and patient safety. Research to understand how the physical and chemical properties of SFs can be most effectively applied to distinguish the SFs from authentic products has not yet been investigated enough. Here, we investigated the usefulness of two analytical methods, handheld Raman spectroscopy (handheld Raman) and X-ray computed tomography (X-ray CT), for detecting SFs among oral solid antihypertensive pharmaceutical products containing candesartan cilexetil as an active pharmaceutical ingredient (API). X-ray CT visualized at least two different types of falsified tablets, one containing many cracks and voids and the other containing aggregates with high electron density, such as from the presence of the heavy elements. Generic products that purported to contain equivalent amounts of API to the authentic products were discriminated from the authentic products by the handheld Raman and the different physical structure on X-ray CT. Approach to investigate both the chemical and physical properties with handheld Raman and X-ray CT, respectively, promise the accurate discrimination of the SFs, even if their visual appearance is similar with authentic products. We present a decision tree for investigating the authenticity of samples purporting to be authentic commercial tablets. Our results indicate that the combination approach of visual observation, handheld Raman and X-ray CT is a powerful strategy for nondestructive discrimination of suspect samples.

INTRODUCTION

In 2015, 128 countries were impacted by pharmaceutical crime, including sale of substandard and falsified medicines (SFs), and the number of incidents in the Asia Pacific Region exceeded 1,000 for the first time.[1–9] The World Health Organization and the European Commission have warned about the danger posed to public health by SFs, and pointed out the need for measures to detect and prevent distribution of SFs.[10–12] The term of falsified medicines means any medicinal product with a false representation of 1) its identity, including packaging, labeling, name, or composition, as regard any of the ingredients including excipients and the strength of those ingredients; 2) its source, including manufacturer, country of manufacture, country of origin, or marketing authorization holder; or 3) its history, including records and documents relating to the distribution channels used.[12] Meanwhile, the term of substandard medicines refers to genuine medicines produced by manufacturers authorized by the relevant National Medicines Regulatory Authority, but which do not meet quality specifications set out for them by the national standards.[10] The U.S. Food and Drug Administration has investigated various analytical methods to discriminate SFs from genuine medical products.[13] Nondestructive analytical technologies that can identify and quantify active pharmaceutical ingredients (APIs) and excipients in pharmaceutical tablets include Raman spectroscopy,[14–18] near infrared spectroscopy (NIR),[19–27] X-ray diffraction,[28,29] nuclear magnetic resonance spectroscopy,[30] terahertz spectroscopy,[31] and chemical imaging with combinations of vibrational spectroscopy and multivariate spectral analysis.[22,25,27,32–35] In particular, Raman spectroscopy provides sharp, characteristic spectral peaks, and therefore Raman spectroscopy is particularly suitable for identifying APIs and excipients in tablets. In addition, handheld instruments are now widely available for Raman[36] and NIR spectroscopies, and devices covering the spectral region from ultraviolet to the infrared.[13] These instruments are suitable for on-site inspection to detect SFs at airports and customs, and to detect substandard medicines at manufacturing sites. Since these instruments are relatively inexpensive and require little or no sample preparation, they are especially suitable for use in low and middle-income countries (LMICs).[37] Further, these methods are nondestructive, so that specimens found in surveys remain available for use as evidence for legal and regulatory purposes.

Information allowing the manufacture of falsified products is readily available. For examples, the contents of the drug product, including the API identity and quantity, and all excipients, are stated in the drug package insert. Other pertinent information, such as the shape, color, special markings, and ID code can also be obtained easily from the drug package insert or website information. Pfizer Inc. has reported the existence of the falsified medicines containing the same effective ingredient as the authentic medicine, and with very similar appearance to the authentic tablets, in the global market.[38] To detect such falsified products, which may be indistinguishable from authentic products visually and chemically, X-ray computed tomography (X-ray CT) can be used to visualize differences in the physical structure of the tablets, such as particle size, uniformity of granules, film coating thickness, and the existence of pores or voids, which may result from differences in the manufacturing process and conditions, or grade of additive. These are important, because defects of physical structure can influence both stability and dissolution properties. Further, X-ray micro-CT is a powerful tool to observe the distribution of elements in tablets by utilizing the difference of the electron density. For example, the distribution of magnesium in magnesium

* Address correspondence to Tomoko Kakio, Analytical Development, Pharmaceutical Sciences, Takeda Pharmaceutical Company, Ltd., Osaka, Japan. E-mail: tomoko.kakio@takeda.com

stearate, an additive used as a lubricant has been visualized by X-ray CT.[39]

In this study, we investigated the effectiveness of handheld Raman spectroscopy and X-ray CT to discriminate SFs from authentic medicines of product A (Blopress Tablets, Takeda Pharmaceutical Company Ltd., Osaka, Japan), focusing on antihypertensive tablets containing candesartan cilexetil as API which is an angiotensin II receptor blocker, because they are widely prescribed worldwide for the treatment of hypertension. Authentic medicines were collected from Japan manufacture. We used generic products collected in China as example of products containing the same API but having differences in the kind of excipients and the manufacturing process. As known falsified tablets, we used falsified tablets from Indonesia, whose outer packaging and press through pack (PTP) packaging were very similar with the authentic medicine, but were inconsistent with those of authentic medicines.

EXPERIMENTAL

Three types of authentic commercial tablets of Product A including 4, 8, and 12 mg of API, together with lactose monohydrate, corn starch, maize starch, carboxymethylcellulose calcium (ECG-505), hydroxypropyl cellulose (HPC-L), polyethylene glycol 6000 (PEG 6000), and magnesium stearate (St-Mg) were used in this study. The weight and size of the 4 mg, 8 mg, and 12 mg tablets are equivalent, as the amount of lactose monohydrate is adjusted according to the weight of API to maintain a constant total weight. Tablets distributed as generic products in China from two different manufactures and two falsified products discovered in Jakarta, Indonesia, in 2011 and 2012 were also used in this study. The falsified products were identified based on visual inspection of the packaging (differences from the authentic product included the color of the printed letters and the printing positions on the surface of the aluminum blister). These falsified products had been collected in different pharmacies in Jakarta, and their distribution was reported to Forensics, Brand Protection, and Investigations. Two types of model formulations of falsified tablets were also prepared by physically mixing the API and excipients, and directly compressing the mixture at a pressure of 11 kN without a granulation process. One of them contained the 8 mg API and lactose monohydrate to make the same total weight as that of the authentic tablets (T-5), and the other contained 8 mg API and all excipients in the same proportions as in the authentic tablets (T-6).

Handheld Raman spectroscopy. All tablets were evaluated with a handheld Raman spectrometer (TruScan®, Thermo Fisher Scientific, Waltham, MA), and chemical equivalence between the authentic product and the other samples was examined based on the similarity of the Raman spectra. The Raman spectrum of the authentic tablets was registered in the instrument as the reference spectrum, and the similarity of the Raman spectra between the authentic tablets and test tablets was automatically calculated and assigned the *P* value. The test tablet is judged "pass" if the *P* value for similarity is more than 0.05 and "fail" if less than 0.05. In other words, "fail" means that the Raman spectrum of the test sample does not match that of the authentic product. The calculation algorithm for *P* value in the instrument has been validated, but has not disclosed and is designed not to be modifiable. We confirmed the validity and the accuracy of the judgment by extracting and examining the raw data of the Raman spectra. If the device encounters a completely different Raman spectral pattern, it stops accumulating data and judges that the *P* value is 0.

X-ray CT and image acquisition. The X-ray micro CT consists of a combination of a high-intensity X-ray generator and a high-resolution X-ray camera. It is capable of observing the three-dimensional (3D) internal structure of tablets at the micron scale, based on the different X-ray absorptions of the constituent materials. The sample is placed on a rotating stage located between the X-ray generator and the X-ray detector. Multiple two-dimension X-ray transmission images are recorded at different sample-rotation angles, and are converted into a three-dimensional image by a tomographic reconstruction algorithm. X-ray tomography measurements of tablets were conducted using a high-resolution 3D X-ray microscope (nano3DX, Rigaku, Japan). The incident X-ray was generated using a rotating-anode generator with a molybdenum target operated at the tube voltage and current of 50 kV and 24 mA, respectively. The temperature was maintained at 22–24°C during data acquisition. The 2,160 lens, which allowed measurements in a 7.12 mm × 5.40 mm field of view with a resolution of 4.32 μm/pixel, was used. Each CT reconstruction was conducted using 1,800 projection shots with an exposure time of 5 seconds/shot. The analyses were done using the nano3D Calc software (Rigaku) and Image.[40]

RESULTS

Figure 1 shows the appearance of each tablet. The 4 mg authentic product A (T-1) is white scored tablets, and the 8 mg dosage strength authentic product A (T-2) is a reddish white scored tablet. An embossed character was observed on the surface of both authentic tablets. The generic Chinese products, labeled T-3 and T-4 were white scored tablets with no embossed character on the surface. Two model formulation tablets, labeled T-5 and T-6, were prepared by direct compression without granulation. T-5 contains 8 mg API and lactose monohydrate in an appropriate quantity to make tablet of the same shape and size as the authentic product A. T-6 includes API and all excipients in the same proportions as the authentic product A. T-5 and

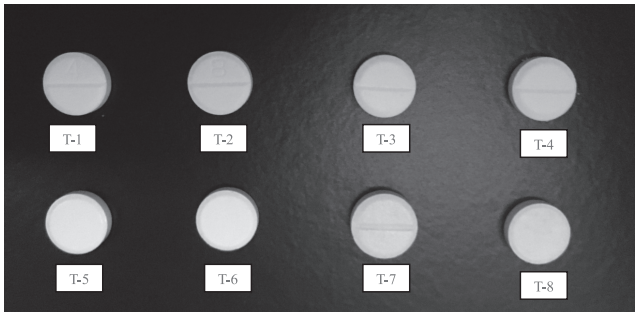

FIGURE 1. Visual inspection of tablets: T-1; authentic product A (4 mg), T-2; authentic product A (8 mg), T-3 and T-4; generic products from different Chinese manufacturers, T-5; model formulation including API and lactose monohydrate, obtained by direct compression, T-6; model formulation including API and the same excipients as in the authentic product A, obtained by direct compression, T-7 and T-8; counterfeits found in Indonesia. This figure appears in color at www.ajtmh.org.

TABLE 1

The results of handheld Raman examination of authenticity, based on the correlation of Raman spectra between test samples and the authentic product A (8 mg).

Number	Category	Sample name (Active ingredient dose)	*P* value	Judgment
T-1	Authentic	Product A (4 mg)	0.2332	Pass
T-2	Authentic	Product A (8 mg)	0.5045	Pass
T-3	Generic	Generic Product B (8 mg) from China	0.2645	Pass
T-4	Generic	Genetic Product C (4 mg) from China	0.1483	Pass
T-5	Model formulation	Direct compression of API (8 mg) and Lactose monohydrate	0.1348	Pass
T-6	Model formulation	Direct compression of API (8 mg) and all excipients	0.1040	Pass
T-7	Falsified product	Falsified Product of product A (8 mg) from Indonesia	0.0000	Fail
T-8	Falsified product	Falsified Product of product A (16 mg) from Indonesia	0.0000	Fail

The result of the instrumental judgment based on the *P* value is also shown.

T-6 were white tablets with no scored line on the surface. The falsified products T-7 and T-8 from Indonesia, where product A is legally marketed were reddish white scored tablets and reddish tablets with no scored line, respectively. Without detailed knowledge of physical appearance of genuine tablets, it would be difficult to distinguish the falsified products simply by visual inspection.

The Raman spectra of tablets T-1 to T-8 were compared with that of the authentic product. Table 1 shows the *P* values and the auto-judgment results for each tablet. The authentic product T-2 was evaluated correctly as "pass" ($P = 0.5045$). Authentic tablets with a different dose of API (4 mg, T-1), the generic tablets T-3 and T-4 from China, and the model formulations T-5 and T-6 including same dose of API as authentic product T-2 were also discriminated as "pass," although the *P* values were lower than that of the authentic product T-2. The falsified products T-7 and T-8 were evaluated as "fail" based on the obvious difference of the Raman spectra from that of the authentic product. These results suggested that the handheld Raman technique can distinguish falsified products that are grossly different from authentic products, but cannot discriminate suspect samples with similar composition including an insufficient quantity of API.

The Raman spectra obtained with the handheld instrument are shown in Figure 2. Samples T-1 to T-6 showed very similar Raman spectra to that of the authentic product. The spectral features are mainly due to the API and lactose monohydrate. Characteristic peaks of the API that do not overlap with peaks due to the excipients were observed in the region from 1780 to 1700 cm^{-1}as shown in Figure 2. The peak intensity from API in this region was reported to increase linearly with increase of API content in the tablets.[28] The Raman spectra of tablets T-1 to T-6 illustrate the difficulty of discriminating authenticity correctly among compositionally similar samples based only on chemical properties. On the other hand, the *P* values of the

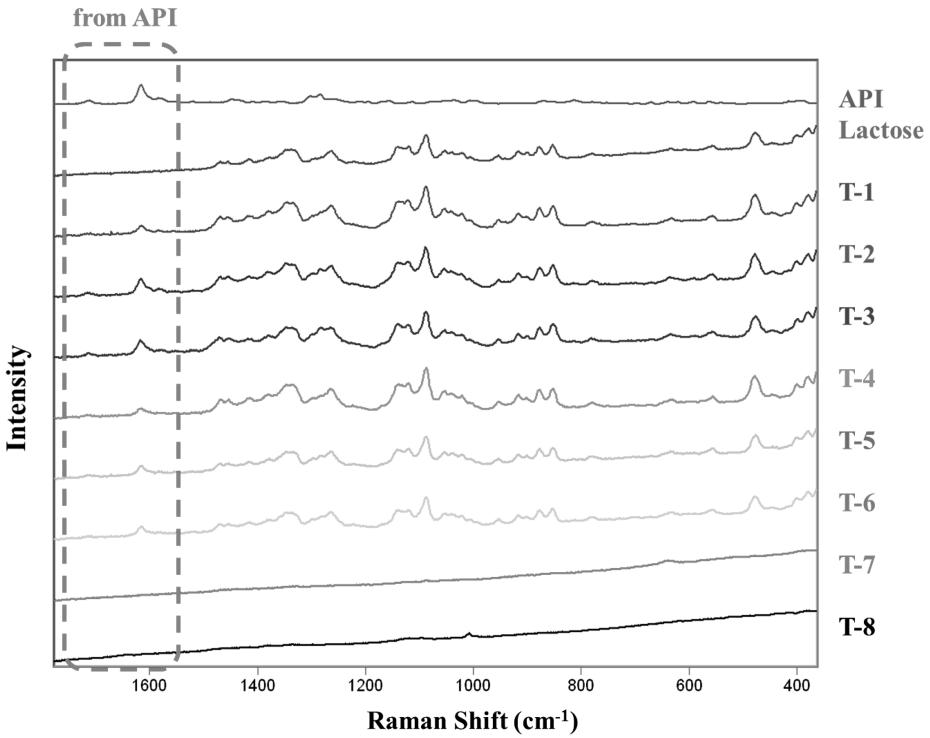

FIGURE 2. The Raman spectra of the active pharmaceutical ingredient (API), lactose monohydrate (excipient) and the tablets. The area surrounded by the dashed line covers the specific peak of API that does not overlap with the peaks of excipients. Other peaks are due to excipients, mainly from lactose monohydrate. The Raman spectra of T-1 to T-6 including both API and lactose monohydrate are similar, but T-7 and T-8 show distinctly different spectra. This figure appears in color at www.ajtmh.org.

falsified products T-7 and T-8 were 0.0000; their spectra showed no characteristic peaks of API, and the baselines rose from higher to lower wavelengths, suggesting the presence of a fluorescent component. Thus, falsified products that do not contain the API can be evaluated correctly as "fail."

Figure 3 shows the average *P* values calculated automatically by the handheld Raman instrument with reference to the authentic product A (8 mg), T-2. Good repeatability of the *P* value was confirmed using three different lots of the authentic product A (8 mg) with 10 replicate measurements. The other doses (4 mg and 12 mg) of the authentic products gave average *P* values of 0.2127 and 0.2725, respectively, compared with the range of 0.5059 to 0.6768 for three different lots of 8 mg product A. These results suggested an appropriate criterion of the *P* value should be set for discriminating the authenticity of the product A (8 mg) from falsified products. Based on the average *P* values, a *P* value of less than 0.4 might be a suitable criterion for judgment of falsified or substandard products containing less than 50% or more than 150% API compared with the content of the authentic product.

Next, samples T-1 to T-8 were examined by X-ray CT, as shown in Figure 4. Uniform granule powders and white spots were seen in images of the authentic products T-1 and T-2. The white spots showed an elongated planar shape and were considered to St-Mg, a known component of the authentic tablets. Magnesium has a high electron density, and therefore has a higher X-ray absorption than the other components, so that St-Mg is clearly visualized in the CT image. The CT image of generic product T-3 showed much larger granules of non-uniform size and pores with a diameter of more than 400 nm. Generic products T-3 and T-4 did not show evidence of the presence of St-Mg. Generic product T-3 showed aggregates with a diameter of 200–600 μm order. The model formulations T-5 and T-6 showed a uniform and smooth appearance, presumably due to the direct compression process without granulation. However, the density unevenness resulting from the lack of enough mixing process is confirmed by the color unevenness as in the black portion of the CT imaging. Also, in the CT imaging of T-5 and T-6, the distribution of the larger particle as seen in T-1 and T-2 are not confirmed.

The images data of falsified product T-7 showed many pores and cracks inside the tablets, suggestive of a poor manufacturing process. The image of falsified product T-8 shows a large amount of an unknown higher specific gravity component dispersed throughout the tablets.

DISCUSSION

Visual inspection of the appearance of a drug product is a critical test item for detecting the falsified products. However, in the present study, falsified products T-7 and T-8 showed a similar color to the authentic product T-2. Thus, instrumental methods are important to identify SFs.

Although the spectrum resolution of the handheld Raman instrument is only about one-tenth in the comparison with the high resolution benchtop instrument, the handheld device is cheap and easily portable for the field use, such as at the airports, customs, manufacturing sites in the developing countries, owing to its small size. This instrument covers the required region of 2875–250 cm^{-1} to observe APIs and some excipients in the tablets. In this study, it was found that the detection and discrimination of the falsified products of the product A were achieved by using the handheld Raman instrument. Although the Raman spectra of tablets T-1 to T-6 were quite similar, the behavior of the repeatability in the same lot and the variation of the *P* value among the lots suggested

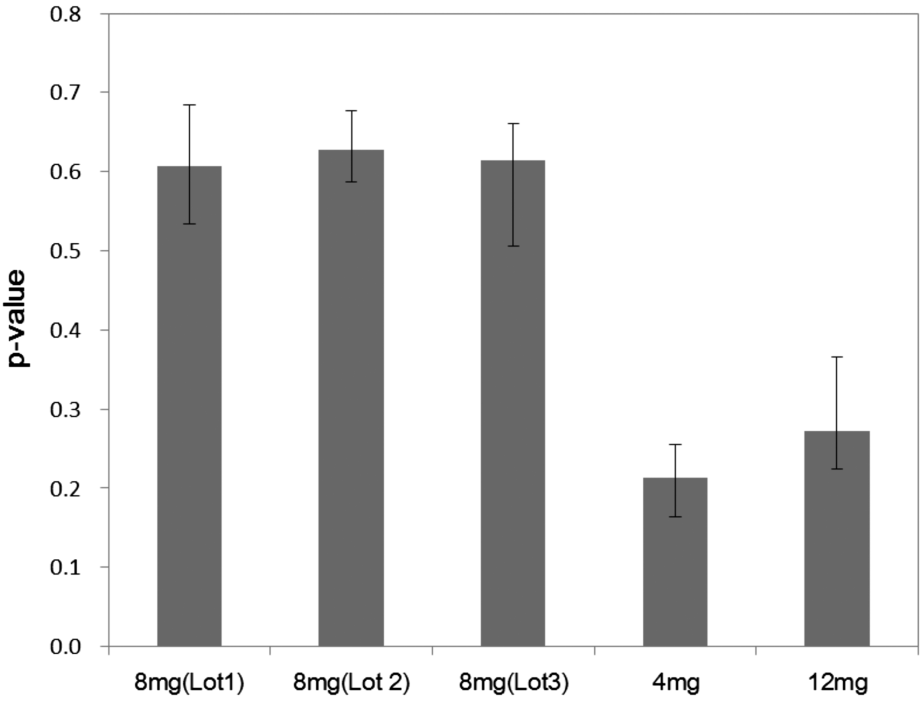

FIGURE 3. Average *P* values of authentic products calculated automatically by the handheld Raman device for similarity to the authentic product A (8 mg). Repeatability of the *P* value was confirmed by ten replicate measurements. The range of the *P* value from the maximum to the minimum value is shown by a bar. This figure appears in color at www.ajtmh.org.

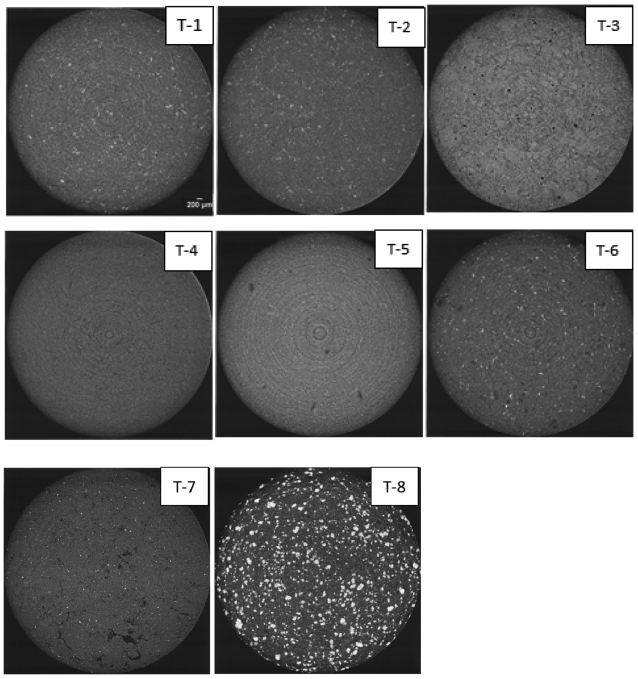

FIGURE 4. X-ray computed tomography images of the internal structure of tablets T-1 to T-8.

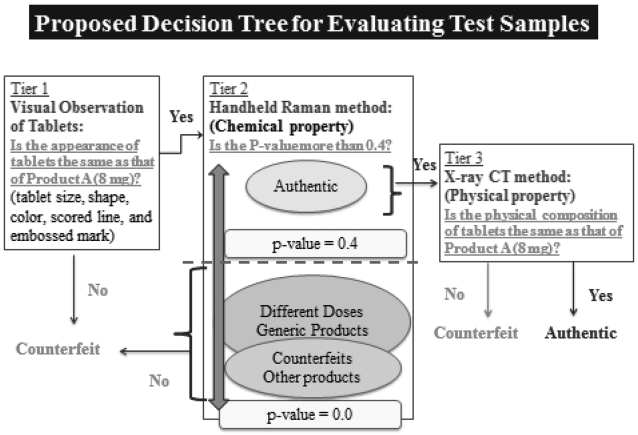

FIGURE 5. Decision tree of combination approach for nondestructive discrimination between test samples and authentic product A (8 mg). This figure appears in color at www.ajtmh.org.

that a criterion *P* value of not more than 0.4 could be used to discriminate SFs. The *P* value was also clearly different among the original product A, the generic products and the model formulations. This difference may be from the difference of the kind of and/or the grade of the excipients and the difference of the manufacturing process. When the suspect sample is evaluated whether it is product A or not, the trend of the *P* value should be considered.

Our results are in agreement with those of a research group in University of Washington (Kovacs et al., 2014), which compared various solutions for detecting SFs in LMICs and evaluated handheld Raman as one of the top solutions, offering multiple advantages, including no need for sample preparation, high performance, speed, ease of use, low cost, no requirement for electricity supply. Further, handheld Raman technology can be used without opening the PTP package, because the laser is focused on the tables, and the peaks from the plastic do not overlap the peaks of API. Therefore, this technology is particularly suitable for on-site inspection throughout the supply chain, such as at custom, posts, airports, and also in manufacturing sites.

The X-ray CT approach enables detailed examination of the internal structure of tablets. Many voids were observed inside the falsified product T-7, while falsified product T-8 contained a large amount of excipients with high electron density. Also, the physical mixture, T-5 and T-6 showed X-ray CT images that were clearly distinct from those of authentic product A, reflecting the omission of the granulation process. Further, generic products which included the same amount of API but contained different excipients and granules of the different sizes could be easily distinguished. The results of X-ray CT of T-1 and T-2 suggested that the API is not identified nor localized in a specific location in the tablets. This is one of the important information about the quality of T-1 and T-2 to discriminate the SFs from authentic samples. Thus, the combination of Raman spectroscopy and X-ray CT can provide detailed information about API content and internal structure and uniformity of the tablet. At present the CT images have to be visually evaluated, but developments in equipment and software should make it possible to score images objectively in the future.

Overall, these results indicate that the combination approach of visual observation, handheld Raman and X-ray CT should be a powerful strategy for nondestructive discrimination of SFs. Figure 5 shows a decision tree for using these combination methods to discriminate the authenticity of samples purporting to be product A (8 mg). The first step is the visual observation of the tablet size, shape, color, scored line, and embossed mark (Tier 1). Next, handheld Raman should be applied to identify the API and to detect differences of the kind of the excipients, based on the *P* value (Tier 2). Generic products and different doses of product A should be discriminated at this point. Then, if necessary, the physical composition of the tablet can be investigated by X-ray CT (Tier 3). This combination approach should enable accurate detection of even falsified products that have very similar properties to the authentic products. Further it should provide detailed information to assist in tracking the source of the falsified products and for monitoring trends in SFs, as well as assessing the efficacy of regulatory procedure.

Received December 10, 2016. Accepted for publication May 9, 2017.

Published online June 19, 2017.

Acknowledgments: We are grateful to Takeda Pharmaceutical Company, Ltd. for supporting this research. We also thank William Bramstedt for supplying samples, Yasutaka Igari and Kenichi Shofuda for help with global collaboration, and Isao Hamanaka and Kensaku Hamada (Rigaku) for the technical support of the X-ray CT measurements.

Authors' addresses: Tomoko Kakio, Kazunobu Moriguchi, Takashi Hiroshima, and Yukihiro Ikeda, Analytical Development, Pharmaceutical Sciences, Takeda Parmaceutical Company Limited, Osaka, Japan, E-mails: kakio.tomoko@gmail.com, kazunobu.moriguchi@takeda.com, takashi.hiroshima@takeda.com, and yukihiro.ikeda@takeda.com. Naoko Yoshida, Hirohito Tsuboi, and Kazuko Kimura, Drug Management and Policy, Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan, E-mails: naoko@p.kanazawa-u.ac.jp, tsuboih@p.kanazawa-u.ac.jp,

and kimurak@p.kanazawa-u.ac.jp. Susan Macha, Takeda Pharmaceuticals USA Inc., Global Product Protection, Deerfield, IL, E-mail: susan.macha@takeda.com.

REFERENCES

1. Pharmaceutical Security Institute, 2016. Available at: http://www.psi-inc.org/geographicDistributions.cfm. Accessed June 19, 2016.
2. Yoshida N, Khan MH, Tabata H, Darath E, Sovannarith T, Kiet HB, Nivanna N, Akazawa M, Tsuboi H, Kimura K, 2014. A cross-sectional investigation of the quality of selected medicines in Cambodia in 2010. *BMC Pharmacol Toxicol 15:* 13.
3. Takahashi N, Tsuboi H, Yoshida N, Tanimoto T, Khan MH, Kimura K, 2013. Investigation into the antinfluenza agent oseltamivir distributed via the internet in Japan. *Ther Innov Regul Sci 47:* 699–705.
4. Kimura K, Honma T, Tanimoto T, Takao C, Okumura J, Yoshida N, Akazawa M, 2011. Public health implications of personal import of medicines through internet brokers (2); buying anti-obesity agents on-line. *Jf Health Care Soc 21:* 55–67.
5. Khan MH, Okumura J, Sovannarith T, Nivanna N, Akazawa M, Kimura K, 2010. Prevalence of counterfeit anthelminthic medicines: a cross-sectional survey in Cambodia. *Trop Med Int Health 15:* 639–644.
6. Khan MH, Okumura J, Sovannarith T, Nivanna N, Nagai H, Tara M, Yoshida N, Akazawa M, Tanimoto T, Kimura K, 2011. Counterfeit medicines in Cambodia: possible causes. *Pharm Res 28:* 484–489.
7. Newton PN, et al., 2001. Fake artesunate in southeast Asia. *Lancet 357:* 1948–1950.
8. Newton PN, et al., 2008. A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS Med 5:* e32.
9. Hall KA, Newton PN, Green MD, De Veij M, Vandenaabele P, Pizzanelli D, Mayfong M, Dondorp A, Fernández F, 2006. Characterization of counterfeit artesunate antimalarial tablets from southeast Asia. *Am J Trop Med Hyg 75:* 804–811.
10. World Health Organization, 2015. *Definitions of Substandard and Falsified (SF) Medical Products*. Available at: http://www.who.int/medicines/regulation/ssffc/definitions/en/. Accessed May 14, 2016.
11. World Health Organization. 2016. *Substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products*. Available at: http://www.who.int/mediacentre/factsheets/fs275/en/. Accessed June 19, 2016.
12. European Union, 2013. European Commission, Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use. *Official Journal of the European Union 56:* C343/01. (2103/C 343/01).
13. Ranieri N, et al., 2014. Evaluation of a new handheld instrument for the detection of counterfeit artesunate by visual fluorescence comparison. *Am J Trop Med Hyg 91:* 920–924.
14. de Peinder P, Vredenbregt MJ, Visser T, de Kaste D, 2008. Detection of Lipitor counterfeits: a comparison of NIR and Raman spectroscopy in combination with chemometrics. *J Pharm Biomed Anal 47:* 688–694.
15. Mazurek S, Szostak R, 2006. Quantitative determination of captopril and prednisolone in tablets by FT-Raman spectroscopy. *J Pharm Biomed Anal 40:* 1225–1230.
16. Mazurek S, Szostak R, 2008. Quantitative determination of diclofenac sodium in solid dosage forms by FT-Raman spectroscopy. *J Pharm Biomed Anal 48:* 814–821.
17. Ricci C, Eliasson C, Macleod NA, Newton PN, Matousek P, Kazarian SG, 2007. Characterization of genuine and fake artesunate anti-malarial tablets using Fourier transform infrared imaging and spatially offset Raman spectroscopy through blister packs. *Anal Bioanal Chem 389:* 1525–1532.
18. Ricci C, Nyadong L, Yang F, Fernandez FM, Brown CD, Newton PN, Kazarian SG, 2008. Assessment of hand-held Raman instrumentation for in situ screening for potentially counterfeit artesunate antimalarial tablets by FT-Raman spectroscopy and direct ionization mass spectrometry. *Anal Chim Acta 623:* 178–186.
19. Dowell FE, Maghirang EB, Fernandez FM, Newton PN, Green MD, 2008. Detecting counterfeit antimalarial tablets by near-infrared spectroscopy. *J Pharm Biomed Anal 48:* 1011–1014.
20. Lopes MB, Wolff J-C, 2009. Investigation into classification/sourcing of suspect counterfeit Heptodintrade mark tablets by near infrared chemical imaging. *Anal Chim Acta 633:* 149–155.
21. Rodionova OYe, Pomerantsev AL, 2010. NIR-based approach to counterfeit-drug detection. *Trends Analyt Chem 29:* 795–803.
22. Puchert T, Lochmann D, Menezes JC, Reich G, 2010. Near-infrared chemical imaging (NIR-CI) for counterfeit drug identification: a four-stage concept with a novel approach of data processing (Linear Image Signature). *J Pharm Biomed Anal 51:* 138–145.
23. Been F, Yves RKD, Esseiva P, Margot P, 2011. Profiling of counterfeit medicines by vibrational spectroscopy. *Forensic Sci Int 211:* 83–100.
24. Xiang D, Lobrutto R, Cheney J, Wabuyele B, Berry J, Lyon R, Wu H, Khan MA, Hussain AS, 2009. Evaluation of transmission and reflection modalities for measuring content uniformity of pharmaceutical tablets with near-infrared spectroscopy. *Appl Spectrosc 63:* 33–47.
25. Xiang D, Berry J, Buntz S, Gargiulo P, Cheney J, Joshi Y, Wabuyele B, Wu H, Hamed M, Hussain AS, Khan MA, 2009. Robust calibration design in the pharmaceutical quantitative measurements with near-infrared (NIR) spectroscopy: avoiding the chemometric pitfalls. *J Pharm Sci 98:* 1155–1166.
26. Rantanen J, Räsänen E, Tenhunen J, Känsäkoski M, Mannermaa J-P, Yliruusi J, 2000. In-line moisture measurement during granulation with a four-wavelength near infrared sensor: an evaluation of particle size and binder effects. *Eur J Pharm Biopharm 50:* 271–276.
27. De Beer T, Burggraeve A, Fonteyne M, Saerens L, Remon JP, Vervaet C, 2011. Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. *Int J Pharm 417:* 32–47.
28. Kakio T , Hiroshima T , Ikeda Y , 2014. Development of quantitative analysis for polymorph of drug substances in pharmaceutical oral dosage forms by XRPD and raman spectroscopy. *J Pharm Mach Eng 23.*
29. Newman AW, Byrn SR, 2003. Solid-state analysis of the active pharmaceutical ingredient in drug products. *Drug Discov Today 8:* 898–905.
30. Holzgrabe U, Malet-Martino M, 2011. Analytical challenges in drug counterfeiting and falsification-The NMR approach. *J Pharm Biomed Anal 55:* 679–687.
31. Shen Y-C, 2011. Terahertz pulsed spectroscopy and imaging for pharmaceutical applications: a review. *Int J Pharm 417:* 48–60.
32. Sacre P-Y, De Bleye C, Chavez P-F, Netchacovitch L, Hubert Ph, Ziemons E, 2014. Data processing of vibrational chemical imaging for pharmaceutical applications. *J Pharm Biomed Anal 101:* 123–140.
33. Stephenson GA, Forbes RA, Reutzel-Edens SM, 2001. Characterization of the solid state: quantitative issues. *Adv Drug Deliv Rev 48:* 67–90.
34. Wold S, Trygg J, Berglund A, Antti H, 2001. Some recent developments in PLS modeling. *Chemom Intell Lab Syst 58:* 131–150.
35. Xiang D, Konigsberger M, Wabuyele B, Hornung K, Cheney J, 2009. Development of robust quantitative methods by near-infrared spectroscopy for rapid pharmaceutical determination of content uniformity in complex tablet matrix. *Analyst (Lond) 134:* 1405–1415.
36. Bakeev KA, Chimenti RV, 2013. *Pros and Cons of Using Correlation Versus Multivariate Algorithms for Material Identification via Handheld Spectroscopy*. Available at: http://www.americanpharmaceuticalreview.com/1504-White-Papers-Application-Notes/147135-Pros-and-Cons-of-Using-Correlation-Versus-Multivariate-Algorithms-for-Material-Identification-via-Handheld-Spectroscopy/. Accessed August 30, 2013.
37. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong K, Stergachis A, 2014. Technologies for detecting falsified and substandard drugs in low and middle-income countries. *PLoS One 9:* e90601.
38. Pfizer Global Security, 2007. *A Serious Threat to Patient Safety, Counterfeit Pharmaceuticals*, Available at: http://www.pfizer.com/files/products/CounterfeitBrochure.pdf. Accessed May 13, 2016.
39. Bruno C, Hancock, Matthew P. Mullarney, 2005. X-ray microtomography of solid dosage forms. *Pharm Tech*. Available at: http://www.pharmtech.com/x-ray-microtomography-solid-dosage-forms-0. Accessed June 19, 2016.
40. Schneider CA, Rasband WS, Eliceiri KW, 2012. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods 9:* 671–675.