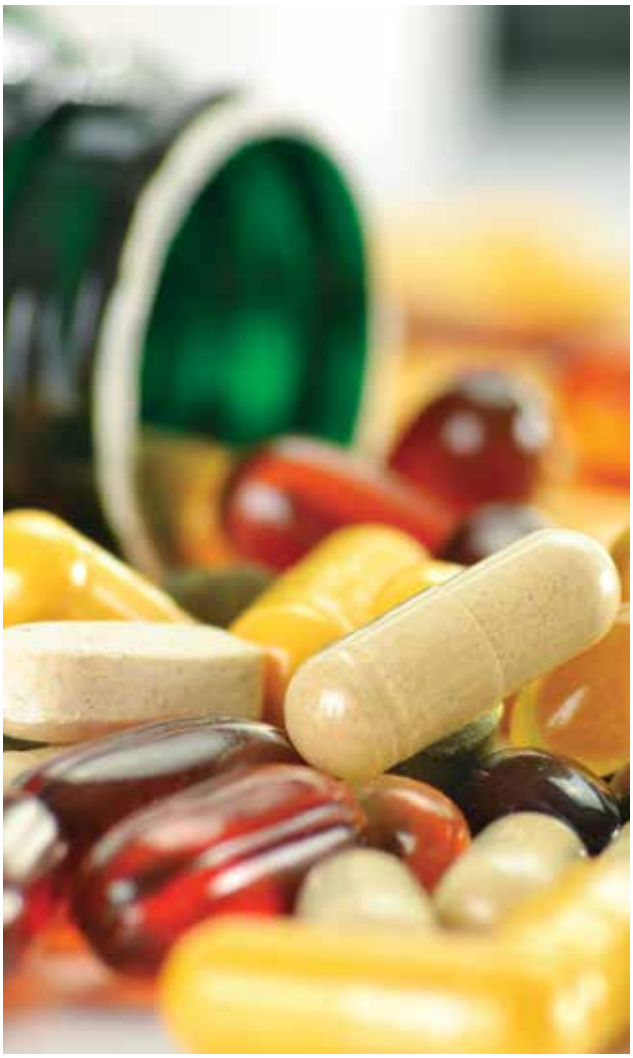
Potential use of handheld Raman devices as tools for screening medicines for quality



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The spread of fake, falsified and substandard medicines is a global threat to public health. The source of most poor quality medicines found globally has been traced to Asia and, although many of these products were found outside the region, many Asian countries are at high risk of exposure to them. Because poor quality medicines are so readily available, there is a need for easy and affordable tools to screen medicines for quality. Handheld Raman devices have gained increasing interest to meet that need. Many of the devices available share some advantages in the detection of counterfeit medicines but also limitations for use in the detection of substandard products. Fixed-dose combination medicines such as some antimalarial products, for example, present an even greater challenge to accurate screening using these devices.

The globalisation of commerce has led to increasing complexity of the medicines supply chain. Preventing the circulation of fake and substandard medicines has become a great challenge to medicines regulatory authorities as well as pharmaceutical companies. Several efforts put in place to counter the spread of such products involve international collaboration. European Directive 2011/62/EU has introduced new measures to prevent the entry of falsified medicines into the legal supply chain in the European Union. Some of its measures require manufacturers of pharmaceutical products intended for the European market to verify the authenticity and quality of the pharmaceutical active ingredients and excipients they use in their manufacturing operations.

Vibrational spectroscopy methods have been used as pharmaceutical quality control tools and, recently, handheld and portable devices have gained popularity in the pharmaceutical industry. Although no single analytical technology could stand alone to carry out quality control testing, the handheld Raman devices have become more attractive as screening tools due to their versatility and portability. Compared to other spectroscopic methods, Raman

does not require sample preparation, chemometric modeling or advanced expertise in its application for material identification. In fact, several companies have developed handheld and portable Raman spectrometers for a host of applications. Many of these instruments have been evaluated as tools to detect fake medicines as well as for use to control the quality of raw materials in pharmaceutical manufacture. Recently, the use of handheld Raman devices in the field as tools to monitor the quality of medicines has gained increasing interest.

Application of Handheld Raman devices for Screening Fixed-dose Combination drugs

Published studies have shown that handheld Raman devices could be a useful tool to detect counterfeit medicines. They have been shown as potential screening tools for detection of products lacking an active pharmaceutical ingredient (API) or having the wrong API. These devices consistently discriminate between different finished pharmaceutical products (FPP) with different APIs or, in some cases, even between different brands.

Several factors can affect the ability of a handheld Raman device for use as a screening tool. For instance, detection limit of the active ingredient is a factor that must be considered when planning to use such a device; that depends on the API Raman scattering. For solid forms, handheld Raman spectrometers generally have a detection limit of 10% w/w, while bench-top portable Raman devices have a detection limit half of that (5% w/w). This limit can be much lower, down to 0.1% for API in solution, thanks to the homogeneity of this dosage form. Fluorescence of the product tested is another factor; fluorescence can overwhelm the Raman signal obtained with the 785 nm laser that most handheld Raman devices use, which greatly affects the detection limit. As shown in Figure 1-A, the Raman

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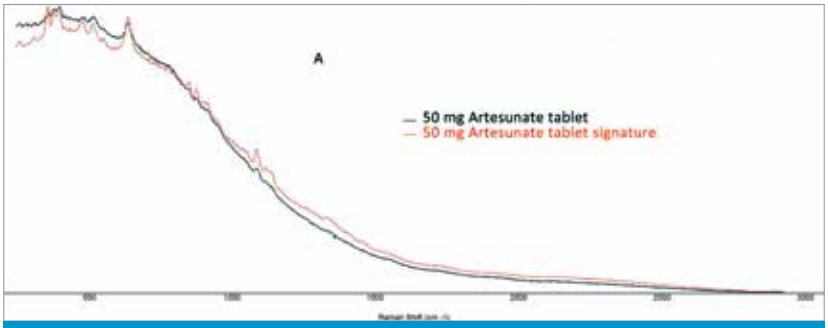

Figure 1-A: Example of the effect of high fluorescence and dosage strength on the precision of a handheld Raman device: Spectra of 50 mg artesunate tablet sample and 50 mg artesunate tablet signature.

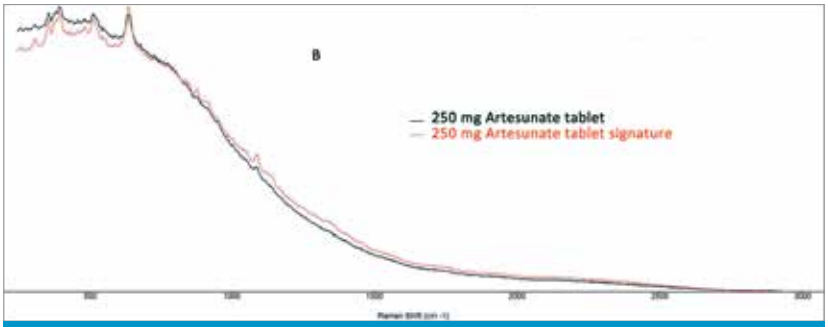

Figure 1-B: Example of the effect of high fluorescence and dosage strength on the precision of a handheld Raman device: Spectra of 250 mg artesunate tablet sample and 250 mg artesunate tablet signature

spectra of a 50 mg artesunate tablet reveals high fluorescence. In this example, spectral matching test of a tablet of artesunate sample against the signature of the same sample was carried out and the sample failed to match to itself. The use of a longer wavelength, such as 1064 nm, may remedy this limitation though the increase of wavelength could reduce the scattering efficiency. Nevertheless, dual band systems could be used for testing a larger spectrum of sample types.

Table 1 provides an example of the effects of fluorescence and strength of the API on the repeatability of spectral matching results obtained with a handheld Raman device. The comparison of twenty tablets of select medicines to the Raman signature of the same product shows that the higher the fluorescence, the lower the number of units that matched the signature. Compared to the results obtained with 50 mg artesunate tablets (75% of tablets matched the signature), the spectral matching test of 250 mg artesunate tablets

Counterfeit Detection Product Showcase - Thermo Scientific

Thermo Scientific TruScan

The family of Thermo Scientific TruScan analyzers represent an important advancement in handheld, portable instrumentation, enabling government and commercial users to effectively “bring the laboratory to the field.”

The Thermo Scientific TruScan has evolved into a powerful tool used at regulatory and donor agencies tasked with ensuring the safety of medicines for the patients in the countries they protect because it can rapidly screen counterfeit pharmaceutical substances on the spot. The device collects a “spectral fingerprint” of the medicine in seconds and compares it to a reference spectrum of an authentic sample from a validated, digital library of medicines and pharmaceutical ingredients.

TruScan analyzers utilize an embedded decision engine containing proprietary algorithms for the comparison. These sophisticated mathematical equations offer a pass or fail result in seconds based upon the statistical consistency of the “spectral fingerprint” with the authentic reference. The digital library can also be easily enhanced by the end user through input of their specific materials of interest.

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Medicine (tablets)	Fluorescence	% Matching to Signature
300 mg acetyl salicylic acid	Low	100
500 mg chloroquine	Moderate	100
50 mg artesunate	Strong	75
250 mg artesunate	Strong	100
300 mg quinine sulfate	Strong	85

Table 1: Example of the effect of fluorescence and dosage strength on the precision of a handheld Raman

indicates that the higher the strength of the API, the higher the precision of the Raman device (Figure 1-B). The difference between the spectra of the two dosage strengths is barely noticeable (Figure 1-A & Figure 1-B).

Handheld Raman devices have the ability to identify APIs in fixed-dose combination medicines by searching through a library containing API signatures; however, if one or more of the APIs are present in a low dose, the device may fail to identify them. For instance, a handheld Raman device consistently identified acetaminophen and aspirin in a product containing 250 mg acetaminophen, 250 mg aspirin, and 65 mg caffeine. When twenty-four (24) tablets were tested against the signature of acetaminophen the device did not identify caffeine as a component of any of the tablets tested. This could be due to the strong Raman scattering of acetaminophen and aspirin overwhelming the Raman signal generated by caffeine. Such effect may also explain the results obtained from testing 500mg-25mg sulfadoxine-pyrimethamine (SP) tablets. Spectral matching of several tablets of SP against the signature of USP sulfadoxine reference standard showed that all the tested samples matched the reference standard; Figure 2 shows an example of this comparison. This result suggests that a handheld Raman device may not be able to detect the absence of pyrimethamine in a fake SP product containing only sulfadoxine as API. Many medicines against infectious diseases are fixed-dose combinations. The suitability of a handheld Raman device for identifying APIs in such products needs to be demonstrated prior to its use. Improvements of detector sensitivity of handheld Raman devices could be part of a solution for their use in carrying out mixture analysis to identify APIs in fixed-dose combination products.

Conclusion

Applications of handheld Raman devices in screening medicines for quality have been limited to qualitative testing. While they have proven helpful in detecting fake

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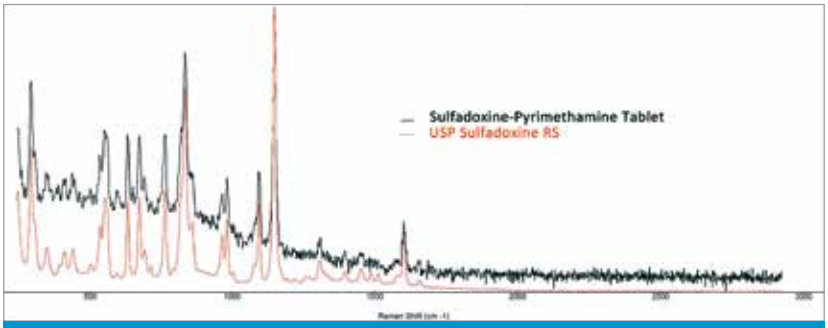

Figure 2: Comparison of 500 mg-25 mg sulfadoxine-pyrimethamine tablet to USP sulfadoxine reference standard.

and falsified medicines, substandard medicines—which are more prevalent—represent an even bigger issue. In addition to treatment failure as potential effect, their use may contribute to the emergence of drug resistance. The use of handheld Raman spectrometers to test substandard medicines would require tedious modeling which neither affordable nor practical for routine testing. Integrating chemometrics into the device as an application, on the other hand, may lead to quantitative use in the future. In addition, researchers from the U.S. Food and Drug Administration have demonstrated that the transfer of spectral library and chemometric-based Raman methods across different Raman handheld devices is feasible.

Handheld Raman devices could easily be used for authentication of starting materials in a manufacturing company set-up as the number of materials to be tested is relatively small. Nevertheless, the methods used to test these materials would have to undergo validation. In a larger setup, such as at a country level, use of such devices as a tool for screening medicines for quality would be far more challenging; for one thing, it would require building a library for all the authentic products entering the country. Handheld Raman devices could be useful in combination with other screening methods to test targeted medicines; however, the suitability of the device for testing such products has to be demonstrated. For instance, medicines regulatory authorities can use handheld Raman devices to screen select products with a known history of being a target of counterfeiters or at risk of being counterfeited.

Counterfeit Detection Product Showcase - SciAps

Inspector 500 1030nm

SciAps has been at the forefront of portable Raman technology for nearly 15 years. Founded in 1997 as DeltaNu, we introduced the Smartphone sized ReporteR, the smallest material identification system designed. SciAps and DeltaNu recently merged and re-established a leading role in commercial portable Raman applications that meet rigorous military and commercial specifications including MilSpec, IP67 and 21 CFR part 11.

We are now pleased to introduce the Inspector 500. The Inspector 500 uses a novel 1030 nm laser source that suppresses background fluorescence. This expands the range of analysed compounds identified and verified including cellulose-based materials, starches, complex proteins, etc. For example, the 1030 nm source allows more than over 40 % of USP materials to be better verified because background fluorescence is suppressed. Moreover 12 % of the USP list can only be identified at a 1030 nm or higher wavelength laser. The 500 features a proprietary detector ideally matched to SWIR Raman wavelengths. It requires less cooling than InGaAs sensors used by 1064 nm Raman units thus less battery power and no fans. The 500 is therefore sealed from moisture and dust. A sealed unit is critical for many pharma applications where the unit must be decontaminated or utilised in a clean room or quarantine environment.

We invite you to contact us for more information or a demonstration of the **New Standard in Handheld Raman.**

http://sciaps.com/inspector-500-1030nm/

Inspector

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They can also target products that are widely used and products with high safety-risk profile. Risk-based pre- and post-marketing surveillance of medicines using appropriate screening tools, including handheld Raman spectrometers, could be of great value. One would expect that the development of quantitative or semi-quantitative Raman-based methods using handheld devices would have a larger application in such a set-up.

Although they need improvements, handheld and portable Raman spectrometers have great potential as tools to screen pharmaceutical starting materials as well as finished pharmaceutical products. In addition to detecting fake and falsified products, their use could expand to include detection of substandard medicines or the adulteration of targeted raw materials and finished products. Their ease of use and requirement of minimal training gives them a clear advantage over wet chemistry methods.

Author Biographies

Mustapha Hajjou *is a Program Manager for PQM at U.S Pharmacopeia Convention. He is responsible for managing activities in several African countries where he provides technical assistance for assuring the quality of medicines. This includes strengthening the capacity of medicines regulatory authorities, national quality control laboratories and health programs*

Patrick Lukulay *is the Vice President of USP's Global Health Impact Programs and program director for the USAID-funded Promoting the Quality of Medicines program (PQM). Dr. Lukulay has more than twelve years of experience in pharmaceutical drug development and analytical research. He has held a number of leadership positions at several pharmaceutical companies.*

Counterfeit Detection Product Showcase - Rigaku Raman Technologies

Over-the-Counter Product Analysis Using Raman Spectroscopy

Similar to pharmaceutical drugs, Over-the-Counter (OTC) products are subject to regulation by the FDA and other Boards of Health, and current Good Manufacturing Practices (cGMP). OTC products are formulated with one or more active pharmaceutical ingredients (API) in a matrix of excipients, binders and other components.
The implementation of handheld Raman analysers for pharmaceutical material detection resulted in a similar use case for identification of OTC products and components.

With Rigaku Raman Technologies' portable and handheld product line of Raman analysers, OTC product materials are identified in seconds. Equipped with 1064, 785 or 532 nm laser excitation, our analyser's open architecture design and adjustable settings enable control over the quality of methods which conclude in reliable and actionable Pass-Fail results.

FirstGuard™ provides manufacturers with a handheld solution to perform rapid verification of a broad range of raw materials. Users can quickly perform accurate, non-destructive analysis through sealed packaging and increase testing to achieve 100% inspection.

Rigaku Raman Technologies' portable solutions include the Xantus-2™, the first portable dual wavelength Raman analyser to enter the market. Equipped with options of 785 and 1064nm or 532 and 1064nm lasers stabilised for Raman spectroscopy, the Xantus-2 delivers a unique combination of high sensitivity and minimised fluorescence.

About Rigaku Raman Technologies
Rigaku Raman is a leading global developer of innovative, portable and handheld easy-to-use Raman instruments designed for efficient and reliable analysis for such key application as pharmaceutical and OTC raw material verification, finished product authentication, anti-counterfeiting and academia.

www.rigakuraman.com/solutions

Counterfeit Detection Product Showcase - B&W Tek

B&W Tek offers a complete line of portable and handheld Raman solutions for material identification and verification. With over 10,000 Raman units already deployed worldwide, we have the knowledge and experience to focus on solution-oriented products that are designed for non-specialists and provide easy, rapid measurements in a matter of seconds.

The NanoRam is a state-of-the-art handheld Raman instrument for non-destructive identification and verification of materials such as APIs, excipients, intermediates, & finished products. Compact and agile, the NanoRam can be used by non-technical users to rapidly identify samples in the lab, warehouse, loading dock or field, helping to eliminate quarantine areas and expedite materials through the manufacturing lifecycle.

The i-Raman series of portable Raman systems is unique for its high resolution combined with field-portability. With these systems, you the get the benefits of a high performance system with the convenience of mobility. This series provides quantitative and qualitative analysis in 532nm, 785nm, and 1064nm options, as well as user-friendly, sophisticated chemometrics software. Our fiber optic sampling accessories make it easy to get results with a wide variety of sample types and sizes. These systems' small footprint, lightweight design, and low power consumption provide research grade Raman capabilities anywhere.

For more information on our complete ecosystem of Raman products, visit **www.bwtek.com/technology/handheld-raman**