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AN IMPLEMENTATION PERSPECTIVE ON HANDHELD RAMAN SPECTROMETERS FOR THE VERIFICATION OF MATERIAL IDENTITY

Bradley Diehl, Chi-Shi Chen, Bronwyn Grout, Jose Hernandez, Seamus O'Neill, Conor McSweeney, Jose Montenegro Alvarado and Mark Smith
Pfizer Inc

This article provides a biopharmaceutical company perspective on implementing handheld Raman spectrometers. The authors from the Process Analytical Sciences Group at Pfizer provide global process analytical technology support for Pfizer manufacturing sites. Each author has actively implemented PAT (Process Analytical Technology) for 10 or more years, incorporating analytical technologies and chemometrics for laboratory and process integrated applications. Given the wealth of analytical experience with many other technologies as the foundation, the overall experience with more recently available handheld Raman spectrometers has been very positive for identification (ID) verification purposes. Their general perspectives on handheld Raman spectrometers are discussed.

A recent market profile article about portable Raman spectroscopy in the May 2012 issue of *Spectroscopy* indicated there are now at least a dozen competitors producing portable and handheld spectrometers; prior to 2006, there were almost no portable or handheld instruments available[1].

Within Pfizer, evaluation of handheld Raman spectrometers began at the end of 2007 and manufacturing sites began implementing in 2008. Since that time, more than 25 Pfizer manufacturing sites have implemented handheld Raman instruments for identification testing. Even within that relatively short four year time period, instrument vendors have increased the capabilities of the instruments to perform more rapid identification analysis while also addressing some of the fluorescence challenges to permit an extension of the materials that can be identified. In fact, with the technology evolution, three different instruments are now being used within Pfizer and a fourth lower cost higher performance spectrometer will likely be used at additional sites or to cover materials not originally covered by the first generation of handheld Raman instruments.

There are a number of reasons that help explain the relatively rapid proliferation of the handheld Raman spectrometers. Some of those reasons are listed below along with supporting commentary.

Specificity

The specificity of the underlying quantum mechanical scattering process provides unique fingerprint spectral features for individual materials to permit direct identification determination. Although basic chemometric algorithms are employed, the resolution provided by current handheld instruments permits taking advantage of Raman's wavelength specific features to keep the chemometrics simple while offering statistically significant specificity. In fact, Raman scattering shifts provide enough specificity to distinguish between many closely related materials and are

capable of distinguishing between polymorphic crystal forms of the same substance. This specificity capability of Raman spectroscopy has been a key motivator for so many innovative instrument companies to develop handheld Raman instruments.

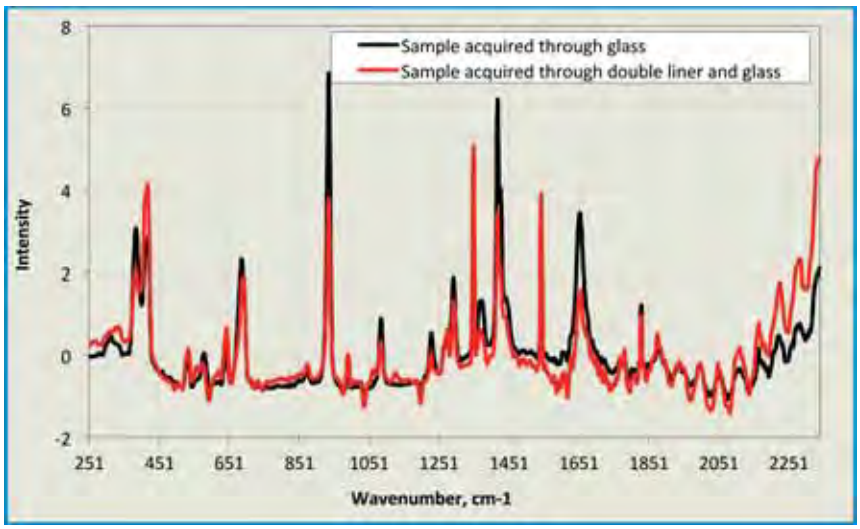

FIGURE 1 Spectral data with Standard Normal Variate (SNV) normalisation applied showing negligible differences for a material when acquiring spectra through only glass vial versus double layer liner plastic and the same glass vial

Pfizer's experience has shown that for Raman active materials, as long as fluorescence isn't a problem with a sample and it has sufficient signal-to-noise ratio to produce a usable spectrum for a material, then there is a very high probability it will be uniquely identifiable. In contrast, our experience has shown that creating identification methods with NIR (Near Infrared Spectroscopy) can require expert effort to select the best regions, algorithm and representative spectra to achieve such specificity. Mid-IR (Mid-InfraRed) methods share similarly good specificity with Raman but typically require some level of sample preparation or direct interfacing efforts, and cannot be used through poly bags.

Minimal interference from relatively transparent plastic

Identification analysis can be performed directly through multiple layers of transparent to partially opaque plastic closure material such as bag liners or bottles with minimal spectral effect. This permits direct identification analysis of incoming materials through liner bags or plastic containers; thus, saving time and avoiding exposure to the materials. This minimal plastic spectral interference helps the methodology to be more robust and less subject to variation at the time of analysis. In fact, colleagues have been successful at collecting reference/library spectra through glass vials and then still effectively verifying the identification of the material through plastic bags (**Figure 1**). However, the best practice is to create reference library spectra in the same container material as used for the routine analysis to enhance the robustness of the identification method.

The capability to perform identification through the bag can be a significant business driver for making use of this technology versus sampling and submission to the laboratory. For instance, one manufacturing site was able to avoid building a specialised sampling room for a toxic material by determining that they could perform identification testing through the shipping bag liner inside a drum. Another manufacturing site discovered several thousand dollars per month of cost savings by simply eliminating the need to purchase vials that would have been used to submit samples to the lab and the costs associated with sample and vial disposals; this was in addition to the labour cost savings of avoiding the sampling, transport and laboratory analysis for identification.

We also have experience creating NIR identification methodologies through relatively transparent plastic bags. For such NIR methods, it is common to remove spectral regions associated with the plastic material in order that the NIR identification methodologies work appropriately. Even then, the NIR method typically shows more variability and less robustness when compared to performing NIR ID testing with glass vial samples. So, in general the handheld Raman spectrometers are more adaptable to identification testing through plastic materials.

> **"Identification analysis can be performed directly through multiple layers of transparent to partially opaque plastic closure material such as bag liners or bottles with minimal spectral effect"**

For situations where the limit of using handheld Raman spectrometers through relatively transparent glass and plastic may be a challenge, the newly available portable (probe head tethered to wheeled instrument) Spatially Offset Raman Spectrometer (SORS) offers the capability to verify identity of materials through some opaque materials (e.g. white polyethylene

FIGURE 2 Section A: Pfizer colleague using handheld Raman instrumentation for through liner scanning in a containment facility in Puerto Rico. Section B: Pfizer colleague using similar instrumentation for through liner and container scanning in Australia

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We also discuss how recent developments in handheld Raman technology will continue to enable wider and faster deployment to achieve the goal of 100% testing of raw materials. Lastly, we discuss the importance of a simplified user interface for non-technical users and how advances in technology have addressed this need.

Presentations include:

- The move to mandatory 100% testing of incoming raw materials
- How handheld Raman improves efficiency
- Recent developments in handheld Raman and reducing costs

Speakers

Ravi Kalyanaraman PhD
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bottles, brown paper, and laminate of paper and plastic). Currently we do not have any experience with these systems, but look forward to learning more in the future about this new technology for niche applications.

Minimal effect in Raman shift signal due to particle size and moisture content

Raman spectroscopy is generally not affected by variations in particle size and moisture content. For purposes as an identification methodology, this is an advantage since the spectral features are more directly related to the chemical composition. Additionally, often only one lot of material is necessary to create the calibration reference spectrum for Raman. This allows users to rapidly create and validate Raman based identification methods. This is an advantage over NIR, which has a best practice of using multiple representative lots of expected material variation to build into the reference spectra library, primarily capturing expected particle size for powders and moisture content variation. However, if conformity verification of particle size and moisture content are important, the NIR capability to discern those characteristics has the advantage and should be done within glass vials to minimise acquisition interfacing variability. Therefore, the choice of techniques is dependent on the intended purpose.

Ease and speed of implementation

The ease and speed of implementation is one of the significant benefits of using handheld Raman spectrometers for identification. This is a direct result of only needing one batch of a material and the high specificity with fit-for-purpose algorithms that makes the generation of identification methods relatively simplistic. It is possible for a manufacturing site to qualify an instrument with straightforward qualification documentation and SOPs, and then validate numerous identification methodologies within weeks. One colleague at a manufacturing plant site validated well over 50 identification methodologies within months of receiving two instruments while also disqualifying additional materials that were not appropriate for the technology. Many readers may recognise that qualification of analytical instruments in the laboratory or a NIR for identification may require much more time. Validation of associated identification methodologies by NIR may extend for many more months or years – especially to achieve more than 50 identification methods.

> “Raman spectroscopy is generally not affected by variations in particle size and moisture content”

Portability

Obviously, the handheld Raman spectrometers are portable. This portability enables easy mobility for calibration and use in a laboratory. But even more so, the portability is beneficial for use in incoming receiving areas. Handheld Raman spectrometers can be easily moved from one container to the next, removed from rooms during cleaning and generally moved wherever there is a need to perform an identification test (**Figure 2**, page 4). If there is a need for maintenance or repair, the instrument can be shipped in an overnight package to the instrument company for those services to be performed. It should be noted that portable handheld NIR spectrometers are also available which provide such benefits.

Transferability

The wavelength accuracy, resolution and resulting specificity along with appropriate use of algorithms and stable electronics permit the transfer of methods between instruments. This has the benefit of permitting the generation of methods on one instrument and then duplication of the methods on a second instrument. Likewise, it can permit instrument replacement without needing to regenerate methods[2,3]. Obviously appropriate validation and documentation is required for transferring methods between instruments.

Ruggedness

Perhaps because of the nature of the intended use, ruggedness is a design aspect being incorporated into the handheld Raman spectrometers. Part of the ruggedness need originates from the large military and emergency responder market applications. There is a chance that the instrument may be dropped, so it needs to be able to survive the drop and continue without any interference with analysis capability. Similarly, the instrument could be in a variable temperature and humidity receiving area; therefore, it is important that the system is also capable of performing in those conditions.

Barcode reading capability

Barcode reading capability is a convenient feature being incorporated with handheld Raman spectrometers. This simple barcode scanning convenience allows the spectra to be linked with product label information and allows the system to be used in an efficient manner while eliminating transcription error potential.

> “Raman spectroscopy is an accepted technology for identification of materials”

Data storage and communications

As would be expected for modern instruments, the handheld Raman spectrometers being marketed provide direct means for storing their data to a computer or network. Some have incorporated wireless communication capability to make backup and storage seamless. From our experience, downloading to Laboratory Information Systems is possible, but requires effort for the interfacing and use of LIMS identifier to be available prior to analysis to automate the process.

Regulatory aspect of the methodology

What about regulatory acceptance? The US and European Pharmacopeia have chapters addressing Raman spectroscopy. Raman spectroscopy is an accepted technology for identification of materials. Our experience is that because of the complexity of submitting filing changes, manufacturing sites may choose to use handheld Raman spectroscopy as an alternative validated method to perform 100 per cent inspection of incoming raw material containers to meet internal or new legislated expectations while still relying on the approved composite sampling plan (e.g. ‘square root of n plus 1’) to perform both registered identification testing plus additional raw material release testing on a smaller sample set.

Business justification

To justify implementation of new technology, it should have underlying business benefit. In this case, business benefit is achieved through the

combination of time savings from usability in receiving areas, not having to open and sample bags, elimination of a need for transporting and logging of samples into a lab, use of a barcode reader to minimise typing, and the elimination of sampling waste (e.g. cost of sample bottle/vial and actual sample material along with cost of disposal). Generally, these are only small incremental cost benefits; however, cumulatively the benefits can be significant for thousands of samples within a month. Therefore, payback period for implementation of a handheld Raman spectrometer can be as short as six months to one year. This means with the relatively short

> "Handheld Raman systems have been widely deployed across Pfizer manufacturing facilities"

implementation times, the instrument can be purchased, qualified, methods validated, put into routine testing and savings recovered all within the same budget cycle. Subsequent years then provide direct cost savings. Implementation across multiple products or manufacturing sites can result in millions of dollars savings per year.

Limitations

Fluorescence from a material or impurity limits the materials that can be identified by Raman. Laser excitation can cause fluorescence to produce enough background to overwhelm any low probability Raman shift for a material. Another limitation is for dark materials. Dark materials absorb the monochromatic light while often not producing a detectable Raman shift. In fact, dark materials are much more likely to also have thermal instability to the laser excitation source used by Raman spectrometers. And obviously, there are some materials without any or only minimal measurable Raman signal.

Nonetheless, second generation instruments are overcoming some of the fluorescence limitations including the use of Fourier Transformation capable handheld instruments.

Summary

Handheld Raman systems have been widely deployed across Pfizer manufacturing facilities. The technology offers many advantages over alternative identification approaches and can be easily implemented with strong business return.

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BIOGRAPHY

Bradley (Brad) Diehl is Manager of PAT Projects at Pfizer in Peapack, New Jersey. His primary role is to engage and facilitate appropriate implementation of PAT at Pfizer manufacturing sites. Brad has 29 years of process analytics experience including applications for products and processes in consumer healthcare, human health, animal health and petrochemical. Brad earned a BA in Chemistry/minor in Biology (Shippensburg University, PA), MBA (University of Tulsa, OK), and MS in Quality Assurance/Regulatory Affairs (Temple University, PA).

BIOGRAPHY

Chi-Shi Chen is Manager in the Development team of the Process Analytical Sciences Group at Pfizer in Peapack, New Jersey. He is responsible for discovering and evaluating new analytical instruments for PAT applications including handheld Raman spectrometers as well as engaging with PAT opportunities for new pharmaceuticals in development. Chi-Shi holds a BS degree in Chemistry from National Taiwan University and a PhD in analytical chemistry from the University of Rhode Island.

BIOGRAPHY

Bronwyn Grout is Senior Manager/ Team Leader, PAT at Pfizer in Peapack, New Jersey. She is responsible for the strategic implementation of PAT for Pfizer's Established Products, Animal Health and Emerging Markets facilities. She has experience implementing PAT for diverse dosage forms for human and animal products. Bronwyn holds a Masters in Science & Technology (University of NSW, Australia) a BSc (honours) in Forensic Chemistry (University of Technology Sydney, Australia) and is currently completing a PhD in Pharmaceutical Chemistry (University of London, England).

BIOGRAPHY

Jose M. Hernandez joined Pfizer Venezuela in 1992 and then moved to USA in 2007 to start working in Process Analytical Sciences Group (PASG) as part of Pfizer's Global Supply Division. He is Senior Scientist, PAT Projects at Pfizer in Peapack, New Jersey. He is responsible for the development, implementation and/or trouble-shooting of pharmaceutical processes using PAT for Pfizer's Emerging Markets facilities. Jose holds a BS degree in Electronic Engineering (Instituto Universitario Politécnico Santiago Mariño, Venezuela) and Post graduated studies in Quality & Productivity Management (Universidad de Carabobo, Venezuela).

BIOGRAPHY

Seamus O'Neill is Director / Team Leader located in Cork, Ireland. He leads a team that supports the implementation of PAT across all sites in Pfizer's Primary Care/Oncology and Speciality/ Biotechnology operating units. Seamus has held roles of increasing responsibility in analytical chemistry within Pfizer and previously in analytical development at Nycomed Amersham, Warner Lambert, Clonmel Healthcare and GlaxoSmithKline. Seamus earned an Honours Degree in Analytical Chemistry at the Cork Institute of Technology in Cork, Ireland.

BIOGRAPHY

José Montenegro-Alvarado is Manager of PAT Projects based at Pfizer in Vega Baja, Puerto Rico. He is currently responsible for technical support and facilitates implementation of PAT at Pfizer's Established Products Sites in Puerto Rico and Australia. Montenegro has over 12 years of pharmaceutical operations experience covering a wide range of fields including process research, capital project management, technical support for pharmaceutical manufacturing equipment and processes, cGMP Validations and PAT installations. Montenegro earned a BS (honours) and MS degrees in Chemical Engineering (University of Puerto Rico at Mayaguez), and holds a Professional Engineer (PE) license.

BIOGRAPHY

Conor McSweeney is Manager of PAT Projects at Pfizer in Cork, Ireland. He is responsible for supporting the implementation PAT at a number of the Primary Care Oncology sites in Pfizer. He worked in the Loughbeg API plant in Ireland as an Analytical Chemistry Specialist from 1998 -2001 and then moved to the Loughbeg Drug product plant and took up the role as Chemistry laboratory Co-ordinator. He then started working with the Process Analytical Sciences Group in 2006 as a Senior Scientist and was promoted to Manager-PAT project in 2008. Conor earned an Honours Chemistry Degree and PhD in Analytical Chemistry from University College Cork.

BIOGRAPHY

Mark Smith is a Senior Manager at Pfizer as part of the Process Analytical Sciences Group based in Cork, Ireland. He is responsible for the implementation of PAT at key sites within Pfizer's Primary Care Oncology operating unit. Mark holds a BSc in Forensic and Analytical Chemistry (University of Strathclyde, Scotland) and a PhD in Pharmaceutical Analysis (University of London, England).

Date
27 – 29 November 2012
Location
Washington DC, USA

Global Forum on Pharmaceutical AntiCounterfeiting and Diversion

The 7th Global Forum on Pharmaceutical Anti Counterfeiting & Diversion will take place this year in Washington DC at the Omni Shoreham Hotel between 27 – 29 November 2012. Sponsored by Covectra, Kodak Security Solutions and Authentix, this is the only event which brings together all the stakeholders in the fight against counterfeit pharmaceuticals.

Since 2002, the Forum has proved to be the agenda setting event covering the most important topics for the industry and this year looks to be no exception. With the increased awareness of the dangers of counterfeit medicines, national drug regulators, law enforcement agencies, international organisations and healthcare professionals have never been more active in the fight against fake medicines and medical devices. Nonetheless, the problem still persists and may even be on the rise in many parts of the world, including the America's and Europe. By bringing together an eclectic mix of stakeholders, delegates will have the opportunity to meet and discuss these issues with some of the leading figures in the US and worldwide public and private sector.

The conference will commence on Tuesday 27 November with a Workshop 'The Challenge of RX Diversion' presented by Dr William Compton, National Institute of Drug Abuse and Charlie Cichon, Executive Director, National Association of Drug Diversion Investigators. The Workshop will be followed by a Seminar on 'The Role of Smartphones in Pharmaceutical Anti- Counter feit and Anti-Diversion Protection', presented by Hugh Burchett and Jon Edgcombe of Cambridge Consultants. Tuesday's events will be completed with a Round Table Discussion on

'Drug Resistance: How Counterfeits Contribute and How to Prevent This'. This discussion will be chaired by Rear Admiral Tim Ziemer, President's Malaria Initiative and Tom Woods, of Woods International.

The Global Forum comprises 25 papers grouped into four thematic sessions:

- Global & Regional Developments
- Prescription Drug Diversion: The Issue and the Fightback
- Technology Developments
- Making it Work

This programme maintains the Global Forum's approach of practical presentations to provide specific and helpful information to all participants, which has contributed to the success of the previous events. Many of the fields' most well respected and established representatives are giving case studies or similar practical presentations, including for example:

- Pfizer
- Reckit Benckiser Pharmaceuticals

As an added bonus for delegates, the keynote speech on Wednesday 28 November at 9.00 am will be given by Robert Hormats, US Under Secretary of State for Economic Growth, Energy and the Environment and his paper, titled The US Contribution to the War on Counterfeit Drugs, looks set to be a magnificent start to this 7th Global Forum.

In addition, the Forum will include a trade show exhibition which will provide the ideal opportunity for delegates to meet and network with suppliers and potential partners from around the globe.

The 7th Global Forum on Pharmaceutical AntiCounterfeiting & Diversion looks set to be an unmissable industr y event. This three day conference will provide the perfect opportunity to network, meet with colleagues and learn from industry peers, many of whom are leading and influential figures in the sector.

FURTHER INFORMATION

Visitors will need to pre-register to attend which can be done via the website www.pharma-anticounterfeiting.com

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PORTABLE RAMAN SPECTROSCOPY FOR PHARMACEUTICAL COUNTERFEIT DETECTION

Ravi Kalyanaraman, Michael Ribick and George Dobler
Bristol-Myers Squibb

Pharmaceutical counterfeiting has become a major global issue in the past decade[1]. This issue no longer pertains only to under-developed and developing countries, but has also placed significant pressure on the assurance of supply chain integrity in developed countries due to increasing global manufacturing and international trade, and also due to sales via the internet[2]. The recent incident of counterfeit Avastin® in the United States demonstrates the vulnerability of the supply chain even in developed countries[3]. Therefore, it is imperative that pharmaceutical manufacturers and government health agencies find ways to fight counterfeit and substandard drugs by identifying them from manufacturing through the supply chain and eventually when they reach the public via distribution channels, e.g., pharmacies and clinics.

One of the effective ways to authenticate a pharmaceutical product is by using Raman spectroscopy to obtain a unique spectral 'fingerprint' of the authentic drug product itself that can be used to evaluate a suspect sample by spectral comparison to determine if it is indeed a counterfeit.

Raman spectrometers have found inroads into the pharmaceutical industry mainly in Process Analytical Technology (PAT) as in-process controls during manufacturing, and in Quality Control laboratories for raw material and finished product identification[4]. More recently, they have been utilised for counterfeit drug identification[5–8].

Technological advancements in the telecommunication diode laser industry[9] and fibre optics, along with advances in optical and detector component miniaturisation, have led to drastic reduction in size of Raman spectrometers and have made them portable. The operation of most of these portable Raman spectrometers is straightforward and intended for a broad user base. They are designed in such a way that the user only needs to point the unit at a sample and push a button to obtain a 'Pass' or 'Fail' result within minutes.

Why portable?

One of the greatest advantages of the portable Raman spectrometer is to take the 'lab' closer to the arena where the counterfeit activities are taking place (such as deceitful manufacturing facilities, pharmacies, hospitals, warehouses and storage facilities etc.). This can provide a level of analytical control in the drug distribution chain, from the manufacturing floor to the retail pharmacies. Also, local law enforcement agencies can use them to detect counterfeits in the field. Samples can be analysed rapidly in a non-destructive manner on-location and the results can be obtained within minutes. This can potentially help the agencies to take immediate follow up steps in the form of seizures or shut down the counterfeit operations in a rapid manner. This is critical since the time taken for samples to be sent to remote testing facilities can be long enough to allow the unscrupulous counterfeiters to flee the site and re-establish operations elsewhere.

FIGURE 1 Output screenshot results in TruScan RM® portable Raman spectrometer

> **" Raman spectroscopy is a technique that provides information on molecular bond vibrations of various functional groups that are characteristic with well delineated absorption bands "**

This article provides two examples of counterfeit products that were detected using the portable Raman spectrometer. In both cases, the output resulted in a 'Fail' when tested against authentic Raman fingerprints. In addition, using the spectrometer's embedded software algorithms, it was possible to identify contents in these counterfeit samples. Typical output screenshot results for a 'Pass' and 'Fail' samples are given in **Figure 1**.

Raman spectroscopy is a technique that provides information on molecular bond vibrations of various functional groups that are characteristic with well delineated absorption bands and therefore are viable for spectral fingerprinting of pharmaceutical drug products[10]. The technique is rapid, nonintrusive and non-destructive, which means that can be used for the analysis of many classes of pharmaceutical dosage forms. The nonintrusive nature of the technique makes it feasible to analyse a drug product directly through the packaging, such as bottles or blisters, and through capsule shells for encapsulated products. Once a suspect sample has been identified as a counterfeit, the non-destructive nature of this technique aids in preserving samples for further investigative work if needed, and can allow the intact sample to be presented in a court of law as evidence, if an action is warranted.

FIGURE 2 Raman spectra of authentic and counterfeit capsule

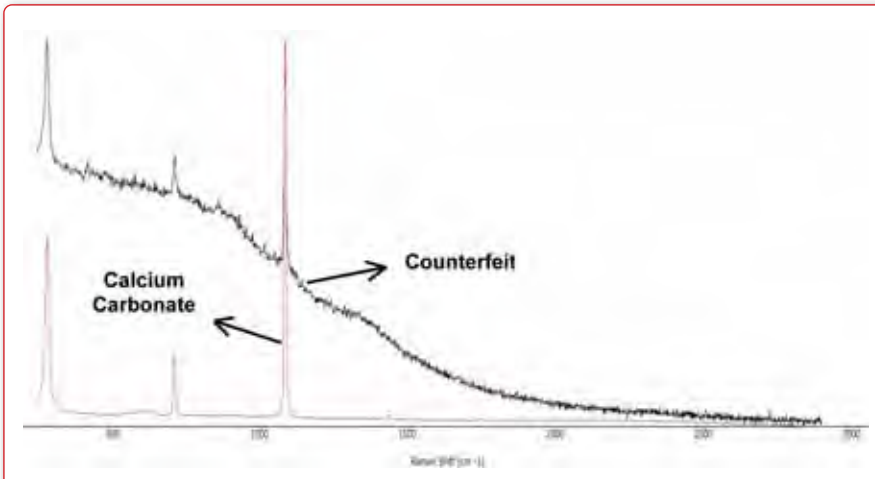

FIGURE 3 Raman spectra of counterfeit capsule and calcium carbonate

Raman spectroscopy is used to study fundamental modes of molecular vibrations using a monochromatic light, usually a laser. The laser light interacts with the sample, in this case a pharmaceutical product, and the scattered radiation is detected to gather information on the product under interrogation. The scattered light is both elastic and inelastic in nature, with the inelastic or Raman scattering

being the one that carries information on the bond vibrations used for spectral fingerprinting. This inelastic scattering is of low efficiency, which acts as an advantage for obtaining spectral fingerprint information without the need for sample dilution or preparation. The spectral information obtained is highly selective and the peaks are sharp, and thus require little or no data pre-treatment. Peaks arising from functional groups such as OH, NH and CH that are present in most pharmaceutical active ingredients and excipients comprise a large portion of the spectral fingerprint for the pharmaceutical product.

The portable Raman spectrometer uses a laser source at a wavelength of 785 nanometres with low laser power (about 250 mW) and low spectral resolution compared to bench-top Fourier Transform units, i.e., 7 to 10 cm^{-1} as compared to 4 cm^{-1} or better, but the lower resolution is still found to be very useful for counterfeit detection. Identification and authentication of drug products are

> **"For the library spectrum, one authentic capsule spectrum was generated and the counterfeit capsule was tested against this library spectrum"**

typically performed by spectral matching of samples under interrogation against the authentic product. The match value for the spectral comparison is given by a probability p-value. The p-value for spectral identification is a measure of how likely the Raman spectrum of a test sample is matched to the signature fingerprint spectrum or reference spectrum. Typically, a p-value less than 0.05 indicates that the sample spectrum has significant differences compared to that of the reference (fingerprint) spectrum. In this case, the sample may be considered as non-authentic. Conversely, for p-values greater than 0.05, it would be assumed that the spectra are sufficiently similar to indicate a match.

Analysis of a counterfeit capsule

It was known from previous tests that this particular capsule sample had the same packaging and appearance as that of the authentic product, but did not contain the active ingredient and proper excipients as the authentic product. Therefore, it is referred to as 'counterfeit' in this article. Both the authentic and counterfeit capsules were tested as is, through the blister pack using the portable Raman spectrometer. The following sections detail the results obtained.

For the library spectrum, one authentic capsule spectrum was generated and the counterfeit capsule was tested against this library spectrum. It is clear that the counterfeit capsule Raman spectral features did not match those of the authentic library spectrum (**Figure 2**, page 12). Also, the p-values for the counterfeit capsules were found to be less than 0.05, which is the default threshold

for a product match in the portable unit. The counterfeit spectrum was found to be consistent with the spectrum of calcium carbonate which was already in the spectral library of the portable unit (**Figure 3**, page 12). Therefore, the portable unit not only was able to detect that the capsule sample is a counterfeit, but also identified that it contains mainly calcium carbonate. This result was further confirmed by performing a calcium carbonate assay using the USP compendial method. It is noteworthy to point out that it took about five minutes to obtain the spectral signature library spectrum and only two minutes to obtain the spectrum of the counterfeit product and to identify that it is indeed mostly calcium carbonate.

Analysis of a counterfeit tablet

It was known from visual appearance that this tablet sample differed in shape to that of the authentic product. Therefore, it is referred to as 'counterfeit' in this article. Both the authentic and counterfeit tablets were tested using a portable Raman spectrometer. The following sections detail the results obtained.

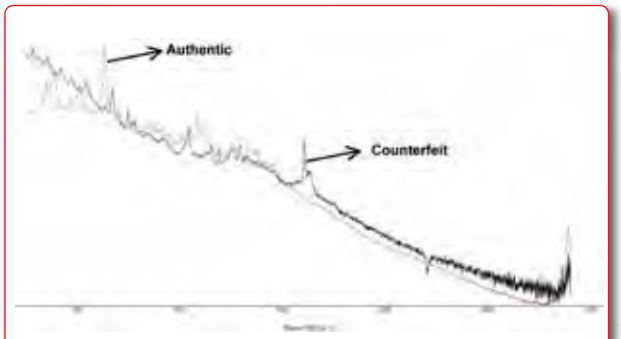

FIGURE 4 Raman spectra of authentic and counterfeit tablet

> "It was known from visual appearance that this tablet sample differed in shape to that of the authentic product"

For the library spectrum, one authentic tablet spectrum was generated and the counterfeit tablet was tested against this library spectrum. It is clear that the counterfeit tablet sample Raman spectral features do not match the authentic library spectrum (**Figure 4**). Also, the p-value for the counterfeit tablet was found to be less than 0.05, which is the default threshold for a product match in the portable unit. The counterfeit spectrum was found to be consistent to spectra of both aspirin and baby powder (talc) spectra which were already in the spectral library of the portable unit (**Figure 5**, opposite). Therefore, the unit not only was able to detect that the sample is a counterfeit, but also identified it as a mixture of mainly aspirin and talc. This result was further confirmed by performing HPLC assay of aspirin and by confirming the presence of talc by bench-top FT-NIR spectroscopy. The analysis times for these tablet samples were similar to those of the capsule sample analysis.

The above two examples clearly demonstrate that a portable

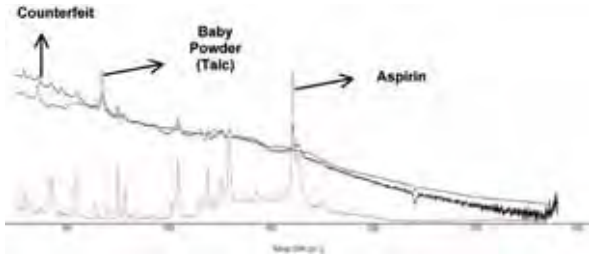

FIGURE 5 Raman spectra of counterfeit and aspirin tablets and baby powder

Raman spectrometer can be used to rapidly evaluate the authenticity of suspect samples and to identify counterfeit pharmaceutical products.

Conclusion

As counterfeit drugs threaten to infiltrate the legitimate supply chain, there is an ever increasing need to find ways to rapidly detect their presence using various means. One effective way to identify them is by using a portable Raman spectrometer to obtain a spectral 'fingerprint' of the authentic product itself, so that suspect products can be screened quickly to determine whether they are counterfeits. The results in this article demonstrate that a portable Raman spectrometer can be used for this purpose and results can be obtained rapidly, and with no destruction to the product. It can potentially be utilised as a screening tool in the field by non-scientific personal, and the decision making process in identifying a counterfeit operation can be vastly improved in terms of time, cost and efficiency.

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NON-DESTRUCTIVE MATERIAL INDENTIFICATION

IN-DEPTH FOCUS

Four Raman experts from the pharmaceutical industry pose one pressing question each for four leading vendor experts in handheld Raman.

Chi-Shi Chen
Manager of PAT Development Projects, Pfizer:

Q Are current pharmacopeia performance expectations for Raman systems appropriate for handheld systems? Can handheld systems satisfy the EP wavelength accuracy tolerances? Is further alignment between ASTM/instrument vendors required to agree appropriate traceable standards for handheld systems for calibration and daily performance checks?

Mark Mabry
Applications Scientist, Rigaku Raman Technologies

A The pharmaceutical industry has capitalised on the use of portable and handheld Raman systems as analysers, not only for raw materials release at the receiving dock, but also to differentiate between commercial products and counterfeit and/or adulterated materials in the field.

Pharmaceutical industry regulatory requirements for the use of Raman spectroscopy are described in compendia such as the *United States Pharmacopeia (USP)* Chapter 1120, or the *European Pharmacopeia (EP)* Chapter 2.2.48, which establishes criteria in the areas of Instrument Performance Control, Wavenumber Axis Verification, Photometric Intensity, Spectral Reference Libraries / Database Selectivity and Analytical Methodology.

Portable Raman systems that are calibrated for both laser and wavelength accuracy by the manufacturer, as outlined in ASTM E 1840-96, should be able to match the wavelength accuracy tolerances specified within *EP* Chapter 2.2.48. In fact, both of these articles provide known spectral references that can be used to calibrate or provide system suitability for Raman systems whether they are portable or laboratory based.

Raman spectroscopy generates data with a high degree of structural selectivity. This, in combination with electronics miniaturisation and ruggedised, high quality optical systems, means that Raman can easily move out of the laboratory and into less controlled environments while still providing specific chemical identification.

It might be useful to increase the number of well characterised wavelength standards but it would be even more useful if instrument vendors and regulatory agencies could establish readily available photometric accuracy standards. This alignment would allow for better comparison between Raman spectra acquired using different excitation lasers and other optical components.

Bronwyn Grout
Senior Manager/ Team Leader, Pfizer:

Q Since the introduction of handheld Raman instruments into the pharmaceutical arena, the number of companies and instrument offerings for the raw material ID application has certainly grown. With this competition, we've seen an improvement of instrument capabilities as well as additional price accessibility in some cases. Can we expect this trend to continue in the years to come or is this instrumentation segment close to reaching the maturity phase of its lifecycle?

Sean Wang
Founder and CEO, B&W Tek

A Generally speaking, the pharmaceutical arena for handheld Raman instrumentation is still in its early sate of adoption, but it is expected to grow continually for many years to come. There are a number of companies attempting to enter into the market, but due to the highly regulated and conservative nature of the pharmaceutical industry, only very few companies will be successful in doing this. We expect that a handful of marginal players will make some waves in the industry, but that only two or three of the most competent suppliers will be able to share in the majority of the market; leaving the marginal players with very little impact.

B&W Tek's success with the NanoRam is a direct result of eight years of Raman knowledge and technology in hardware, software and most importantly, chemometrics development. Our infrastructure and experience in serving and supporting more than 9,000 deployed Raman instruments worldwide has really set the stage for providing a total customer experience for NanoRam customers in the pharmaceutical industry.

While the NanoRam is set at a modest and affordable level, the true value we are offering is that of low cost of ownership as well as easy installation and compliance. This technology represents a significant improvement of handheld Raman technology, and we are in the process of implementing this change in the field. From here, we expect improvements that are heavily focused on software (i.e. improving signal processing, method development and transfer, and chemometric analysis) while incremental hardware advancements will continue to further pave the way for these software improvements. All of these improvements will increase the adoption rate of handheld Raman, which will inevitably drive down the cost, allowing for further price accessibility.

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ASK THE EXPERT

Ray Horton
Pfizer:

Q In the API (active pharmaceutical ingredient) world, fluorescence hasn't been too much of an issue for handheld instruments as the majority of raw materials work really well. However, for drug product excipients it is more of a challenge; celluloses, silicates and brightly coloured dyes are a few of the materials where the Raman hasn't worked for us. Some progress has been made to eliminate the impact of fluorescence, how well is this progressing? Will it be possible to eliminate the interference from fluorescence completely?

Rick Cox
Director of Business Development, Applications & Marketing, DeltaNu

A Competing fluorescence can be eliminated from the Raman spectrum in a few ways. Some baseline correction methods can remove gradual slope changes in the Raman spectra; however, intense fluorescence can completely overwhelm the Raman information. In this case, we provide one micron systems for highly fluorescent samples. These systems were limited by the size of the detectors based upon class IV semiconductors which required intense cooling. Most recently these detectors operate with good performance under moderate cooling specifications (-20°C to 10°C) that make them attractable for portable systems. Our portable systems use a diode pumped 1030 nanometre Yb:YAG in our new Inspector Raman.

DeltaNu's InspectoR 785

The InspectoR 785 system works very well for measuring microcrystalline cellulose. We have demonstrated this with distinguishing different types of cellulose using our Advantage 1064 nanometre Raman system.

Tony Moffat
Emeritus Professor of Pharmaceutical Analysis, UCL School of Pharmacy:

Q It is often important to retain the integrity of packaging and yet analyse the contents of containers. It is also much faster to analyse intact articles. How does your SORS technology achieve this?

Darren Andrews
Director – Analytical Products, Cobalt Light Systems Ltd

A Raman spectroscopy hasn't been used for that long in RMID but it has quickly become embedded in many companies because of its chemical selectivity and ease of use. However, for conventional Raman to work you need a clear plastic or glass container; where the packaging is opaque and/or coloured – as most containers in Pharma tend to be – testing becomes more complicated, slower and more expensive. For powdered materials, the container must be opened and sampled/ probed, which requires an expensive and time-consuming trip to a laminar flow booth. Safe powder handling requires every container to be opened, tested/sampled and re-sealed by hand before the booth is cleaned to remove any potential contamination.

Spatially Offset Raman Spectroscopy (SORS) is the only technology that enables sample ID through sacks, tubs, bottles and other containers, whether plastic, paper, glass or woven. By measuring spectra at different points on the container (the spatially offset part) SORS measures a Raman spectrum of the contents free from fluorescence or Raman signature of the container – enabling ID through several millimetres of opaque packaging material.

Our SORS instrument, RapID, typically takes between five and 15 seconds to complete a measurement and report a simple pass or fail ID result. A sack of lactose with two brown paper layers and a plastic liner is typically verified in about 15 seconds on the warehouse floor whilst the sacks are unopened on the pallet. One hundred sacks would take about 40 minutes to complete.

In Europe, where 100 per cent verification is required (will the US follow suit soon?) the testing burden is increasingly expensive and opening the packaging can be a significant chunk of the total cost. SORS is ideal for high volume testing, verification of sterile materials (which carry a premium price and have a shorter shelf-life once opened) and for hazardous materials.