# Solutions for Accelerated Raw Materials Identification

Reducing the turn around time and cost of pharmaceutical raw material quality control

# Through-Container Verification of Pharmaceutical Raw Materials with the Agilent Vaya Handheld Raman System

**Accelerate testing throughput without increasing costs.**

Frédéric Prullière

## Overview

The Agilent Vaya Raman system enables rapid raw material verification testing through transparent and non-transparent packaging. Vaya is the first handheld Raman spectrometer incorporating Spatially Offset Raman Spectroscopy (SORS), which allows the testing of incoming goods quickly in the warehouse without the need for sampling or opening containers, thereby saving costs and resources. Raw material verification in a pharmaceutical current Good Manufacturing Practices (cGMPs) environment is typically time consuming and labor intensive, yet the Vaya system takes only seconds per sample. Moreover, its ease of use is amenable to non-spectroscopists with minimal training.

## cGMP Raw Material Verification

### Traditional verification methods

Raw material identification (RMID) in a GMP environment is a mandated process used for the verification of incoming materials in order to ensure the quality of the finished product. Currently, when goods arrive at a company's loading dock, they must be moved to a quarantine area where the containers are inspected for visual defects and the shipping manifest is examined to confirm that it matches the received materials. After these preliminary checks, a statistical number of containers will be chosen for further analysis. For parenteral drugs manufacturing organizations or organizations adhering to strict Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidance, all containers must be analyzed.

Figure 1. Vaya handheld Raman system

The containers are then moved to a dedicated area for sampling. It is common for a powdered raw material to be packaged in a primary container, usually a plastic liner, which is then held inside a secondary container such as a cardboard box, plastic drum, or bucket. For sampling, all of the primary and secondary containers must be opened, which adds considerable time and effort to the analytical process. Powders in multilayer paper sacks are especially tedious, as it is difficult to avoid making a mess and potentially exposing employees to hazardous chemicals. Regardless of the packaging, sampling booth staff must suit up in appropriate Personal Protective Equipment (PPE) to mitigate the hazards of the raw materials. Closing and re-sealing all of the primary and secondary containers, imposes an additional burden.

The sampled materials are placed in vials, which must be labeled and then sent to a quality control (QC) laboratory, where they will be added to a queue for Fourier Transform Infrared Spectroscopy (FTIR) analysis. The remaining raw materials are returned to the quarantine area to await the analytical results. Once the FTIR laboratory has confirmed their identification, the raw materials will be released into production. The RMID process typically takes several days.

If the primary container is transparent, conventional handheld Raman spectroscopy can be used to analyze the raw material. However, this still requires the secondary container to be opened and re-sealed. Although it offers some time savings, it does not avoid the use of a sampling booth and associated consumables, paperwork to enable container opening, its cleaning and maintenance, logistical movements to and from it.

## Optimized verification method

The revolutionary Vaya handheld Raman system detects materials through opaque packaging; thus, it can be used in the quarantine area without opening the containers. Materials delivered to the loading dock are transported to the quarantine area, quickly tested there, and released. Figure 1 shows its ease of use for the identification of raw materials in a paper sack; the instrument is simply aimed at the container and its contents are verified with the push of a button. There is no need for transporting and opening containers, sampling, sealing the containers, or sending samples to a QC laboratory. The simplification and acceleration of raw material verification compared to conventional analysis is illustrated in Figure 2. Distinctively, Vaya reduces RMID time for large batches from several days to just hours.

Keeping containers closed eliminates employee exposure to hazardous chemicals while preserving the shelf life of air-/moisture-/light-sensitive materials. Furthermore, as SORS enables faster ID of raw materials, warehouse management can hold less inventory to meet production demand, and materials can be released more rapidly to answer production peaks. The QC laboratory benefits as well, with shorter queues and additional time for complex analyses.

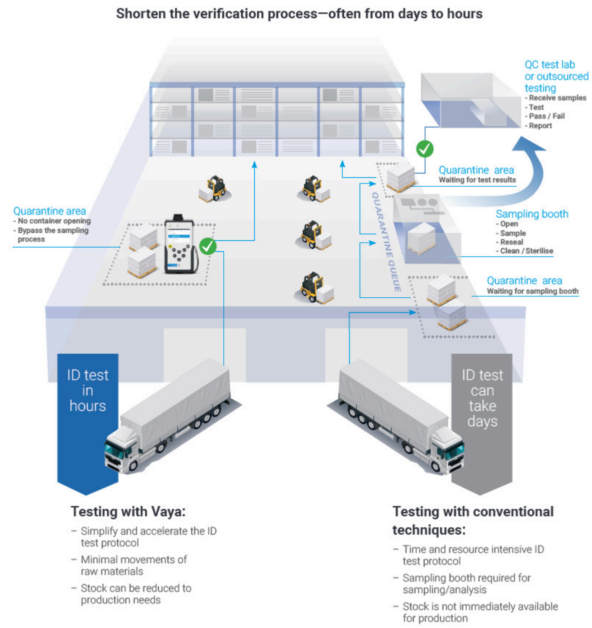



**Figure 2.** Accelerated raw material verification compared to conventional analysis.

## Spatially Offset Raman Spectroscopy (SORS)

Vaya's benefits are derived from SORS technology, which is a patented Raman spectroscopy-based technique from Agilent. It uses the property of light propagation through diffusely scattering media in combination with Raman spectroscopy to achieve through-barrier analysis. Unlike conventional Raman back scattering set-ups, SORS introduces a physical offset between the area irradiated by the monochromatic light and the area of detection. In the offset geometry, because of light traveling effects, the Raman photons collected in the detection area originate mostly from the subsurface layers and yield a spectrum rich in subsurface information. In contrast, a spectrum with no or "zero" offset yields a spectrum rich in the top layer information. Figure 3 Illustrates the SORS methodology applied to the identification of raw material through a container. The diagram on the left shows a scaled subtraction of the container-rich zero offset spectrum, while the middle diagram shows the raw material rich-offset spectrum.

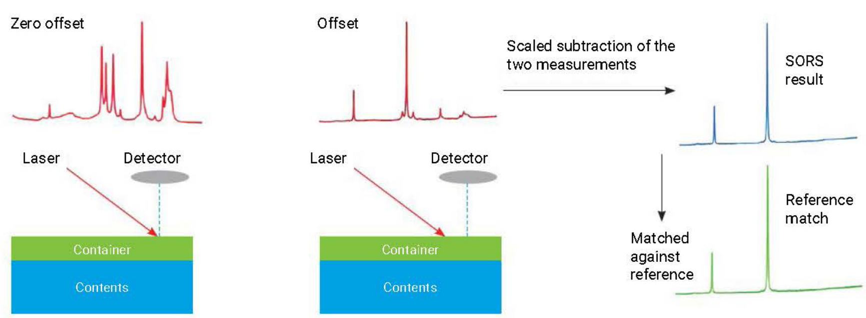
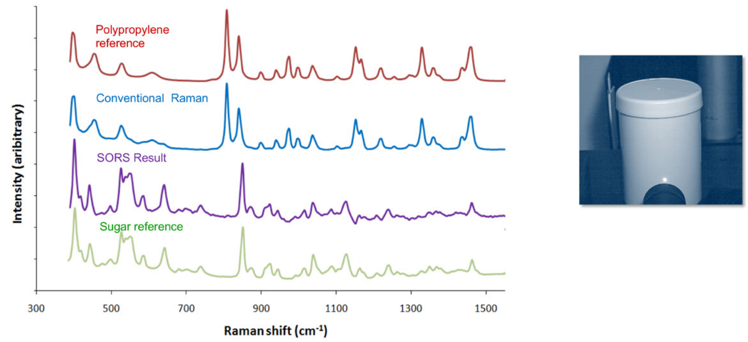



**Figure 3.** Spatial Offset Applied to Raman spectroscopy: the SORS principle.




- Sucrose not identifiable by conventional Raman
- Example of complex spectrum extracted by SORS in 30 sec

**Figure 4.** Sucrose in 1.5mm polypropylene container.

> "SORS is well-suited to a GMP environment for several reasons. It is fast, acquiring a spectrum in a matter of seconds, while demonstrating specificity."

Figure 4 demonstrates the power of SORS technology. Shown in blue, a conventional Raman measurement of sucrose in 1.5 mm white polypropylene yields a spectrum for the plastic container, while the sugar is undetected. In contrast, a 30-second SORS analysis, shown in purple, identifies the contents as sucrose, and matches the gray reference spectrum.

SORS is well-suited to a GMP environment for several reasons. It is fast, acquiring a spectrum in a matter of seconds, while demonstrating specificity. It is also easily validated and can follow the USP <1225> or ICH Q2(R1) validation protocols. Furthermore, SORS is accepted by Compendia because it is a Raman spectroscopy-based technique. There is little to no chemometric support needed over time for warehouse applications, and methods can be readily modified to address changes, for example, in container or supplier.

## The Vaya SORS Raman Instrument

The Vaya is a handheld SORS Raman spectrometer for the ID verification of solids and liquids. The lightweight, battery-powered system can scan through transparent containers just as conventional Raman. Its innovative SORS technique, however, allows it to acquire raw material spectra through opaque containers. This makes it especially beneficial in high-demand verification areas with varied sample types.


**Figure 5.** Key hardware features of the Agilent Vaya Raman System.

## Hardware

The special features of the Vaya are shown in Figure 5. The distinct, brightly colored laser button promotes safety as a dedicated switch for triggering the scan. In addition, an LED light indicates when the laser is firing, and a laser warning is displayed on the screen. Fluorescence is minimized by the use of an 830 nm laser. A NIST-traceable system check test piece enables the user to quickly complete a performance qualification (PQ) to ensure that the instrument is working properly. For practicality, the strap provides ergonomic handling and the instrument is chemically resistant, facilitating easy clean up. The front of the device contains a barcode scanner for quick input of sample and method information. This can also be performed manually via simple keypad steps. Data transfer is straightforward with the incorporated Wi-Fi. The zero and offset measurements are performed automatically, making adjustment of the laser beam unnecessary. The hardware and software of the Vaya are specifically designed for easy use by non-spectroscopists.

## Software

For simplification, users are guided through instrument operations with on-screen animations as well as wizard-based method development. Pass/Fail answers are obtained in seconds, with minimal training. Immediately after acquisition, users can look at a spectrum on the screen of the device and see how well it fits to a reference spectrum.

The instrument's batch mode capability permits users to run multiple samples of the same raw materials and generate a common report for that particular batch. The Progress tab shows the batch's status, including how many samples have been analyzed and the number of passed and failed samples. The convenient Work in Progress (WIP) option allows a batch to be started, stopped, and then resumed later, even in a different shift by a different user.

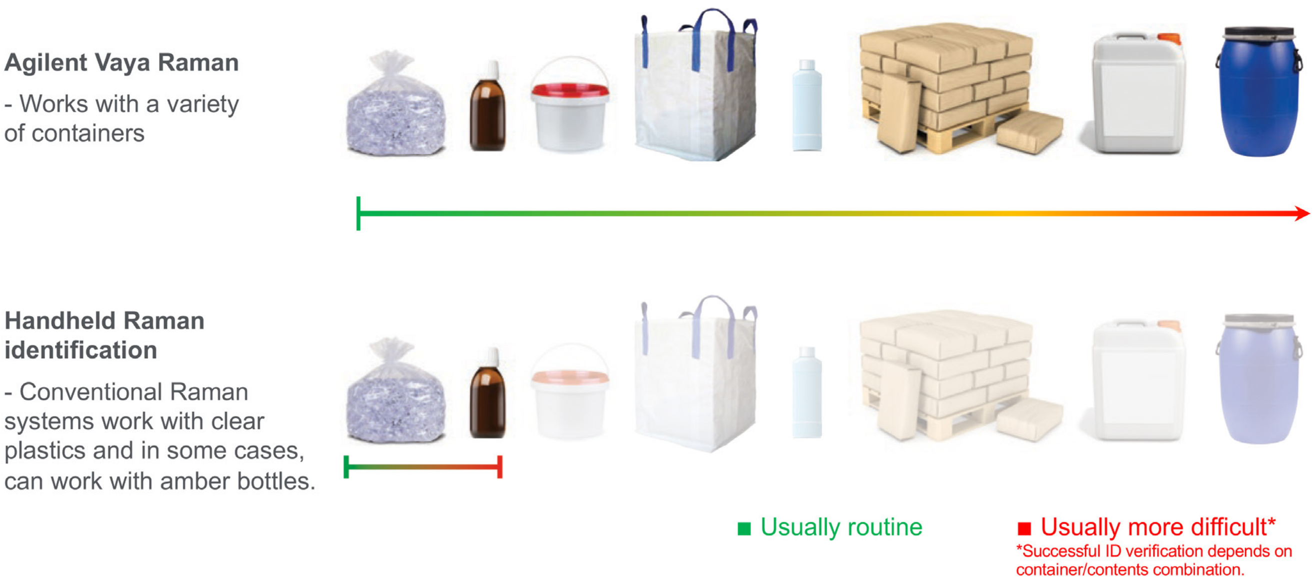



**Figure 6.** Container compatibility.

"Periodic performance verification of the Vaya using the system check test piece will enable the user to demonstrate compliance on an as-needed basis."

Developed for applications within the pharmaceutical industry, the Agilent Vaya system and software are set up to help users meet the stringent Good Manufacturing Practices (GMP) requirements. In particular, the Vaya features functionalities such as user access control and data integrity logics to support compliance with the FDA 21 CFR Part 11. The Vaya meets Raman Spectrometer specifications imposed by the United States Pharmacopeia (USP) general chapter USP<858> and USP<1858> and European Pharmacopeia (EP) chapter EP 2.2.48, necessary for use in the pharmaceutical industry.

Periodic performance verification of the Vaya using the system check test piece will enable the user to demonstrate compliance on an as-needed basis. Method development and validation modules on the Vaya support scientists in developing identification methodologies meeting specificity and robustness requirements of USP<1225> and/or ICH Q2 (R1).

Productivity is enhanced with the barcode scanner, LIMS integration, and synchronization of acquired data with a local area network (LAN) for expedient data management. Readily searchable data folders and human readable files are available, including PDFs for audit trail, batch reports, single scan training, and method and validation reports. SPC files enable viewing of spectral data.

Conveniently, RMID methods can be shared across multiple instruments, and no desktop software is required. Methods are automatically uploaded in a master folder located on the network for backup and sharing. Users can then download methods from the master folder and easily revalidate them for compliance.

## Applications

Perfect for warehouses with GMP operations, the Vaya has wide applicability for different materials and containers. Figure 6 illustrates the container compatibility of the Vaya compared to conventional Raman instruments. With the Vaya system, raw materials can be directly analyzed through plastic liners, amber bottles, multilayered white and brown paper bags, colored and opaque plastics, large flexible intermediate bulk containers (FIBCs), and in some cases, thick blue drums. The Vaya compensates for opacity, thickness, folds, and other variations in primary containers.

An excellent example of the benefit of Vaya's SORS technology is demonstrated in Figure 7, in which citric acid is identified in white polyethylene in just a few seconds. The zero measurement, shown in red, clearly represents the container and not its contents. In stark contrast, the offset measurement in green appears to be rich in citric acid with a small amount of polyethylene. Subtracting the zero spectrum from the offset spectrum results in the blue SORS spectrum at the top of the figure. This is a clean citric acid signal that can be compared to a reference to verify the container's contents.

Analysis of ethylenediaminetetraacetic acid (EDTA) in a brown paper sack is shown in Figure 8. Excessive noise characterizes the red zero spectrum, and extremely weak Raman signal for cellulose whereas the offset and SORS spectra are distinct representations of EDTA in green and blue, respectively. Clearly, the offset measurements in SORS technology offer a significant advantage over traditional Raman analyses by mitigating interference from containers.

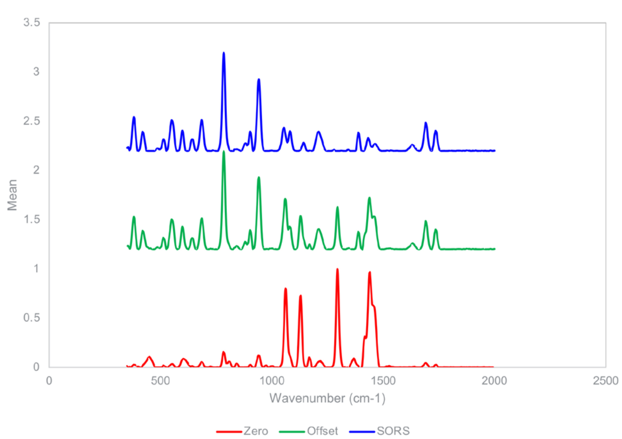



**Figure 7.** Detecting citric acid through a white high-density polyethylene container.

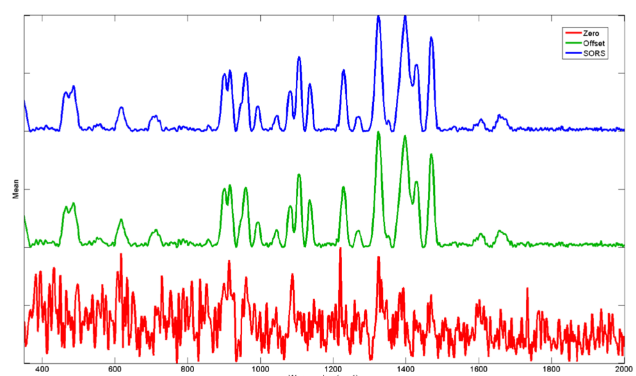



**Figure 8.** Detecting ethylenediaminetetracetic acid through a brown paper sack.

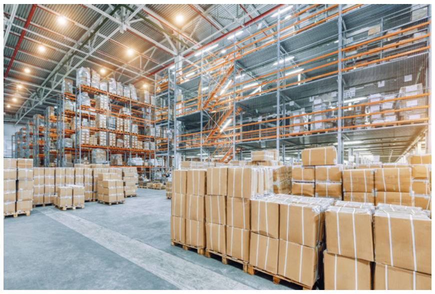
Table 1. Comparative cost study for identifying 1200 samples per month using the Vaya system versus a conventional handheld Raman system

| Task | Process Hours with | | |
|---|---|---|---|
| | Vaya | | Conventional Raman |
| | In quarantine | In booth | In booth |
| Number of samples[1] | 720 | 480 | 1200 |
| Container movements (15 min per raw material consignment moved to/from sampling booth) | 0 min | 900 min | 2250 min |
| Container handling (1.2 min per container – opening, resealing, labeling) | 0 min | 576 min | 1440 min |
| Scan time (Vaya in quarantine 0.75 min/Vaya in booth 0.45 min/Conventional Raman 0.55 min per sample)[2] | 540 min | 216 min | 660 min |
| Sampling room (50 min prep and clean up time per raw material consignment) | 0 min | 3000 min | 7500 min |
| Total time per year in hours | 1,047 Hours[2] | | 2,370 Hours |
| Total cost per year[4] | $36,808 | | $83,320 |
| Cost-per-sample | $2.5 | | $5.80 |

## Vaya's Time and Cost Benefits

The Vaya is the fastest handheld identity verification solution available. For example, it can verify lactose monohydrate in a three-layer paper bag in 80 seconds with no sampling and no mess. Citric acid in a white HDPE bottle can be identified in 15 seconds. It drastically simplifies the RMID process by enabling almost instantaneous screening of incoming containers on arrival, verifying the identity of raw materials in quarantine with a single operator. The time and cost involved in unnecessary movement of containers, sampling booth clean up, sampling utensils, and PPE for testing personnel are all significantly reduced or eliminated.

A time/cost analysis comparing the Vaya system with a conventional handheld Raman system was performed, based on a medium-sized pharmaceutical organization receiving 150 consignments per month of raw materials, representing a total of 1200 samples per month (eight containers verified per consignment). Figure 9 compares raw material identification tests using a Raman handheld device to the same tests using the Vaya system. In the warehouse, any tests requiring the opening of the container were performed in a sampling booth. When the identification could be performed through the container without opening it (using the Vaya), the analysis was conducted in the quarantine area. Only the staff hours were included in this study.



“By simplifying the ID process, the Vaya offers a cost-effective alternative to current conventional Raman-based solutions.”

The table shows that the cost-per-sample and RMID process time are reduced by more than 55% over a one-year period by avoiding the sampling booth and decreasing container handling and transportation. With the Vaya system, all of the consignments can be mixed with production stock within a fraction of one work shift, so that raw materials can be made available for production on the same day they are received.

In addition to saving employee time, significant savings are realized by the need for less PPE, lower stock levels for the warehouse, and lower spending on cleaning accessories. Moreover, if regulators require increased testing, the Vaya supports higher throughput without the need for additional equipment or people. By simplifying the ID process, the Vaya offers a cost-effective alternative to current conventional Raman-based solutions.

## Conclusion

Verification of raw materials is remarkably expedited with the Vaya handheld Raman spectrometer. By automatically taking offset measurements in addition to zero measurements, the container signal can be subtracted to reveal pure spectra for the container's contents. Due to this SORS advantage, the Vaya is capable of obtaining clean signals for materials through a much broader range of containers than conventional handheld Raman instruments.

GMP warehouses typically spend days on raw material identification, including transporting containers, sampling their contents, testing, sealing, returning them to a quarantine area, and waiting for test results. Vaya's SORS technology allows materials to be analyzed easily through their sealed containers in the quarantine area in just seconds, by non-spectroscopists. Keeping containers sealed avoids the potential for contamination and spoilage of raw materials, in addition to protecting employees from hazardous chemical exposure. As such, the Vaya boosts safety as well as productivity.

In addition to the batch mode and Work in Progress features, the automated report generation and networking capabilities of the Vaya streamline every workflow. As the first handheld Raman spectrometer with SORS technology, Vaya greatly simplifies raw material verification while dramatically increasing operational efficiency and reducing costs.

## End Notes

[1]Assumption: Vaya works through non-transparent containers, and this is assumed to be 60% of all incoming materials. For containers that do not work with Vaya, the ID is performed with Vaya in a booth, container opened through the plastic liner.

[2]Scan times derived from an average time to run weakly and strongly raman active raw materials through liners and non-transparent containers.

[3]Sum of time for analysis performed in quarantine and in booth for Vaya.

[4]Operator annual salary: $45K with 1.5 overhead multiplier.

# Identifying Raw Materials Inside Containers Using a Handheld Raman Spectrometer

Reducing the cost of quality with the Agilent Vaya Raman system.

Frédéric Prullière and Oliver Presly

## Overview

With profit margins in the pharmaceutical industry under ever increasing pressure, manufacturing groups are incentivized to achieve First Time Quality (FTQ) and reduce costs.

The identification of raw materials, a current Good Manufacturing Practice (cGMP) mandated process (*1, 2*), is typically resource- and time-intensive and therefore an excellent target for improvements and cost-out efforts.

The Agilent Vaya Raman system is a handheld spectrometer capable of identifying raw materials through transparent and opaque containers. This white paper discusses some of the benefits of deploying the Vaya system in a pharmaceutical warehouse, to simplify and accelerate the ID verification of raw materials at receipt.

To address ever-growing pharmaceutical supply chain challenges and maintain quality standards, regulatory bodies mandate the verification of raw materials before use in production. Up to 100% of all received raw material containers must be checked for identity.

For solid raw materials packaged in paper sacks, tubs, FIBCs/big bags, paper sacks, tubes, bottles, and barrels, ID verification is a multistep process. It starts by unloading raw materials from the truck and moving them to the quarantine area. There, after visual inspection, a proportion of all the containers (up to 100%) are moved to a sampling room. In the booth, after garbing up, an operator opens the container or secondary, outer packaging. The raw material is then verified directly through the transparent primary package using a conventional hand-held Raman spectrometer. If this is not possible, the material is sampled to be analyzed using a Raman device, or sent to a QC lab for mid-IR/NIR analysis.

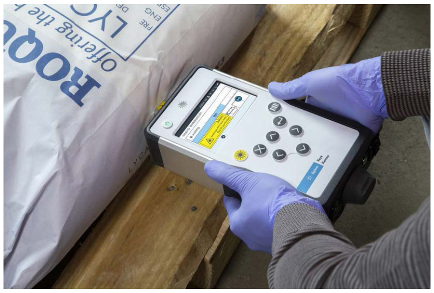


**Figure 1.** Vaya identifies raw materials through multilayer paper sacks

For most QC labs, this protocol is time- and resource-intensive and therefore not cost effective. It is also not scalable or flexible enough to absorb increases in testing or new combinations of raw materials/containers.

## SORS

Spatially Offset Raman Spectroscopy (SORS) is a unique solution from Agilent Technologies that enables the verification of raw materials through containers. SORS improves the depth of penetration of conventional Raman spectroscopy. By leveraging the property of photon propagation inside diffusively scattering media and separating the laser illumination area from the light collection area, SORS can acquire a raw material-rich spectrum. A container-rich signal can be collected when the laser illumination and light collection areas coincide. The scaled subtraction of the container-rich spectrum from the raw material-rich spectrum yields a container-free raw material spectrum. This can be used for identifying pharmaceutical APIs and excipients directly through transparent or opaque containers. Raw materials can be identified without sampling or opening secondary, outer containers. SORS works with opaque packaging like paper sacks, FIBCs/big bags, polyethylene tubs, drums and other containers.

## The Agilent Vaya Raman System

The Vaya is a handheld SORS-based spectrometer from Agilent (Figure 1). The Vaya is the fastest handheld identity verification solution available. For example, it can verify lactose monohydrate in a three-layer paper bag in 80 seconds. Citric acid in a white HDPE bottle can be identified in 15 seconds with no sampling and no mess. It drastically simplifies the identification process by enabling almost instantaneous screening of incoming containers on arrival. The Vaya system can verify the identity of raw materials in quarantine with a single operator. Unnecessary movement of containers, sampling booth clean up, sampling consumables, and PPE for testing personnel are all reduced.

## Cost comparison between handheld Raman systems and Vaya

A small case study easily demonstrates the power of the Vaya system and how pharmaceutical manufacturers can benefit from true raw material identification at receipt.

In this study (Table 1), a time/cost analysis comparing the Vaya system with a conventional handheld Raman system was carried out. The analysis was based on a medium-sized pharmaceutical organization receiving 150 consignments per month of raw materials, representing a total of 1200 samples per month (eight containers verified per consignment). Table 1 compares performing raw material identification tests using a Raman handheld device to performing the same tests using the Vaya system. In the warehouse, as per this company's materials receiving procedure, any ID tests requiring the opening of the container are performed in a sampling booth. When the ID test can be performed through the container with no container opening (using the Vaya), the analysis is conducted in the quarantine area. Only the staff hours are included in this study.

**Table 1.** Comparative cost study for identifying 1200 samples per month using the Vaya system versus a conventional handheld Raman system.

| Tasks | Process Hours with | | |
|---|---|---|---|
| | Vaya | | Conventional Raman |
| | In quarantine | In booth | In booth |
| Number of samples[1] | 720 | 480 | 1200 |
| Container movements (15 min per raw material consignment moved to/from sampling booth) | 0 min | 900 min | 2250 min |
| Container handling (1.2 min per container – opening, resealing, labeling) | 0 min | 576 min | 1440 min |
| Scan time (Vaya in quarantine 0.75 min/Vaya in booth 0.45 min/Conventional Raman 0.55 min per sample)[2] | 540 min | 216 min | 660 min |
| Sampling room (50 min prep and clean-up time per raw material consignment) | 0 min | 3000 min | 7500 min |
| Total time per year in hours | 1,047 hours[2] | | 2,370 hours |
| Total cost per year[4] | $36,808 | | $83,320 |
| Cost per sample | $2.5 | | $5.80 |

Bypassing the sampling booth and decreasing container handling and movements lowers the cost-per-sample and the ID process time by 50% over a one-year period. Using the Vaya system, daily arrivals of raw materials are easily manageable as testing only takes 35 min per consignment in this scenario. All received consignments can be mixed with production stock in less than 5 hours, in comparison to ~10 hours with a conventional handheld Raman solution. With the Vaya, raw materials can be made available for production on the same day they are received.

## Increasing your throughput capability without increasing your costs

Regulatory requirements change, as do quality and testing needs. The Vaya system future proofs the identification protocol by keeping costs low even with high sample volumes. If the quality department requires an ID test on all containers (100% ID) to meet regulatory requirements in countries like Japan or Korea, costs would go up from $36 K/year to $74 K/year[5] with the Vaya. If a conventional Raman system was being used, the costs would rise from $83 K/year to $142 K/year. The Vaya can achieve 100% ID at a cost lower than that for √N+1 testing performed with conventional Raman. If regulators require increased testing, the Vaya allows you to develop higher throughput testing without any additional equipment or people.

Figure 2. The Vaya verifies the identity of acetic acid in an opaque plastic container.

The Vaya can have a positive impact on less obvious expenses too. Using the Vaya in a warehouse helps decrease the stock levels needed to meet production requirements. Reduced stock means lower inventory carrying costs. Savings will depend on how frequently the inventory is used during the year and its cost. A simple reduction of 5% can translate to >$5 K/year for an inventory stock worth $0.75 M6 and immediate first year savings of >$35 K.

Sampling booth expenses can also be reduced. In the booth, an operator is required to use a disposable garment at a cost of ~$10 each, face mask ~$0.2 each, and disposable sampling utensil ~$1.5 each.7 These required items can quickly add up to a saving >$10 k/year. Use of other disposable items like cleaning accessories is also reduced with the Vaya.

By verifying ID directly through the container, the Vaya system helps preserve inert packaging conditions and maintain the expiration date of raw materials (Figure 2). For air-sensitive materials like polysorbates, it means that materials can be fully used before the expiration date instead of being discarded. This alone can easily translate into savings >$100 per tested container.

## Vaya return on investment

The study calculated a return on investment (ROI) when transitioning to the Vaya system over a four-year period from a different handheld Raman solution (Figure 3). For the ROI calculation, deployment costs of the Vaya system, including preparation, method development/validation, were factored into the start up costs. Over a four-year period, for an initial investment including method development/validation and start up costs of ~$115 K in the first year, the Vaya had a net value of ~$114 K or a 61% ROI.8 If the Vaya system is purchased to address a transition to 100% ID, the ROI almost doubles to 107% with a net value of $191 K. The Vaya system is therefore an effective investment to reduce the cost of raw material identification and address increased testing volumes without increasing costs.

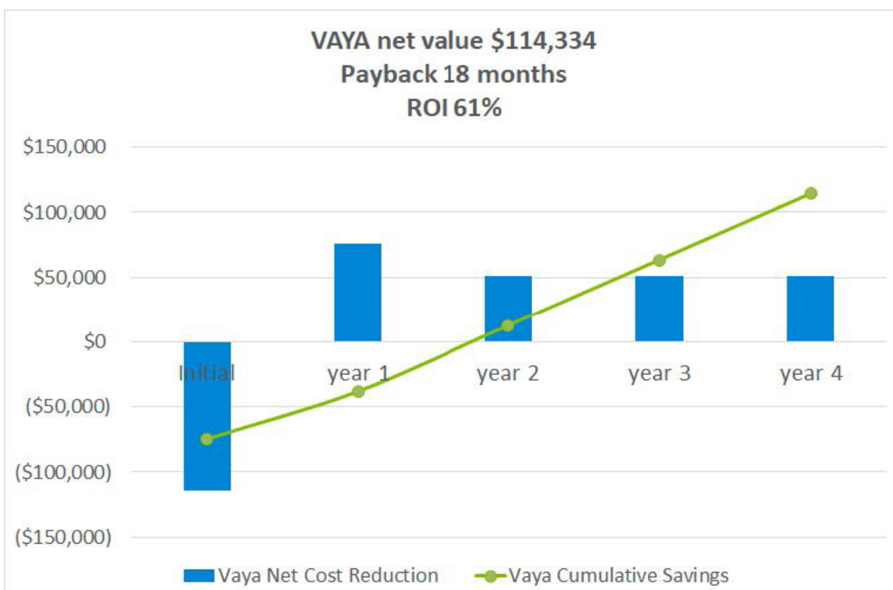



Figure 3. Return on investment when transitioning to the Vaya system from a conventional Raman handheld solution over a four-year period.

## Conclusion

With the Vaya system, it becomes possible to inspect and identify raw materials immediately at receipt. No container handling, no container opening required, and no compromise to sterility. By simplifying the ID process, the Vaya offers a cost-effective alternative to current conventional Raman based solutions. Using the Vaya makes the identification test easily scalable to meet 100% ID requirements and production demands. It also future-proofs your ID protocol against regulatory changes or more stringent quality requirements. Without sampling, you can test more materials for the same cost, or perform multipoint of your raw material containers.

## References


1. Title 21 Code of Federal Regulations, part 2.11.84.
2. EU GMP Annex 8: Sampling of Starting and Packaging Materials


## End Notes

[1]Assumption: Vaya works through non-transparent containers, and this is assumed to be 60% of all incoming materials. For containers that do not work with Vaya, the ID is performed with Vaya in a booth, container opened through the plastic liner.

[2]Scan times derived from an average time to run weakly and strongly raman active raw materials through liners and non-transparent containers.

[3]Sum of time for analysis performed in quarantine and in booth for Vaya.

[4]Operator annual salary: $45K with 1.5 overhead multiplier.

[5]Assumption: The sampling booth is large enough to accommodate 40 containers. If not, additional container movements would need to be added.

[6]With a 15-20% inventory carrying cost.

[7]List prices.

[8]Net present value (NPV) applied for the calculation of the ROI.

# Identifying Raw Materials Directly Through Paper Sacks

Using a handheld Vaya Raman spectrometer to reduce the time associated with identifying materials.

Frédéric Prullière

## Overview

Papers sacks are often used as primary or secondary containers for raw materials employed in the manufacturing of pharmaceutical products. Their enduring popularity continues, as they can easily be disposed of or be recycled to minimize the impact on the environment. They are also the most cost-effective way to package and ship high-volume raw materials. Excipients like lactose monohydrate, mannitol, microcrystalline cellulose, and sucrose are often supplied to pharmaceutical manufacturers in multilayer paper sacks.

The Agilent Vaya Raman system is a handheld spectrometer capable of identifying raw materials through transparent and opaque containers to simplify and accelerate the receipt of raw materials in GMP environments.

This case study highlights how the Vaya instrument can be used for the identification of raw materials through paper sacks in a pharmaceutical warehouse.

Magnesium stearate, microcrystalline cellulose (MCC), mannitol, sucrose, and lactose monohydrate are commodities often used as fillers or excipients for oral solid dosage. These materials are typically received in paper sacks for easy handling and discarding.

At receipt and before use, these excipients must have their Identities verified in compliance with regulatory requirements.

On arrival, the excipients in paper sacks are unloaded from the truck and moved to a quarantine area in the warehouse. Following a visual inspection, up to 100% of the received paper sacks are moved to a sampling booth where they are opened and sampled. Next, the samples are analyzed either directly in the booth with a handheld Raman or NIR system, or they are sent to a QC lab for analysis with FTIR or wet chemistry methods. Once sampled/analyzed, the paper sacks are sealed and moved back to the quarantine area to await approval for release to production stock. This process is time and resource intensive and can take days to complete (Table 1).

**Table 1.** Time required for FTIR and conventional handheld Raman tests for identity verification of 200 paper sacks of lactose monohydrate.

| Department/Task | | Process Hours with | |
|---|---|---|---|
| | | FTIR Performed in the Lab | Conventional Raman Handheld in the Sampling Booth |
| QC | Preparation of sampling container labels | 0.5 | 0.5 |
| Warehouse | Movement of containers from quarantine area to sampling booth | 0.5 | 0.5 |
| QC | Paper sack opening | 1.5 | 1.5 |
| QC | Sampling | 1 | 1 |
| QC | Paper sack resealing | 10 | 10 |
| Warehouse | Movement of containers from sampling booth to quarantine | 0.5 | 0.5 |
| QC | Confirmation test | 33.5 (counting waiting time) | 1.7 |
| Total | | 47.5 hours (Booth clean up not included | 14.7 hours (Booth clean up not included) |

## Verifying Through Paper Sacks

The Vaya instrument uses Spatially Offset Raman Spectroscopy (SORS), a unique Agilent solution, to verify the identity of raw materials through unopened non-transparent containers like paper sacks (Figure 1). Testing can be performed directly in a quarantine area.

SORS uses a pharmacopeia method—using the chemically-specific fingerprint to identify a raw material inside the container. Using the property of photon propagation inside diffusively scattering media, SORS generates a container-free Raman spectrum of the raw material to enable verification against a known reference.

## Experimental

To demonstrate the performance of the Vaya instrument, SORS spectra of a variety of excipients were acquired through paper sacks and compared against their respective references acquired through thin polyethylene liners. The excipients magnesium stearate, microcrystalline cellulose, sucrose, and mannitol were used. All products were supplied by Sigma-Aldrich UK. SORS spectra were acquired for each material in two types of sacks: a three-layer paper bag (one white outer layer, two brown inner layers with a polyethylene liner) from DFE Pharma, Goch, Germany and a two-layer brown paper bag with a polyethylene liner from Meggle Group, Wasserburg, Germany. Scan time for each SORS spectrum was recorded. Reference spectra were acquired in conventional back scattering mode by measuring a thin polyethylene liner. This reference spectrum was then subtracted from the sample spectrum to eliminate any container contribution to the reference spectra.

Figure 1: Using the Vaya Raman instrument to identify contents through a multilayer paper sack.

## Results and discussion

### SORS can identify materials through paper bags

Figure 2 shows how the “polyethylene plastic liner” (i.e., reference) spectra can be easily overlaid with their corresponding “through paper bag” or SORS spectra for all excipients in both paper sacks. By producing a content spectrum free of container interferences, the Vaya instrument can easily verify the identity of a raw material through multilayer paper bags.

### Vaya can identify large batches in hours rather than days

Table 2 lists the scan and process times for the verification test performed for each excipient. The Vaya instrument can verify identity through multilayer paper sacks in 90 seconds or less. Using this approach in quarantine reduces the identity verification process time by a factor of >3 when compared with conventional Raman handheld systems in a warehouse and by a factor of >9 for FTIR in a QC lab. Time-consuming steps like paper sacks sealing, sampling booth clean up, and container handling are eliminated.

Using the Vaya instrument for excipient analysis in paper sacks enables warehouses to shorten their material identity verification process and release materials the day they are received.

### Vaya can identify material directly in quarantine and bypass the sampling room

Using the Vaya instrument, the integrity of the paper sacks is preserved during the analysis. Materials can be identified outside the sampling booth. The approach also eliminates the need for costly consumables like disposable booth garbs and sampling utensils such as vials and thieves. The Vaya instrument enables QC to identify raw materials at the lowest cost possible.

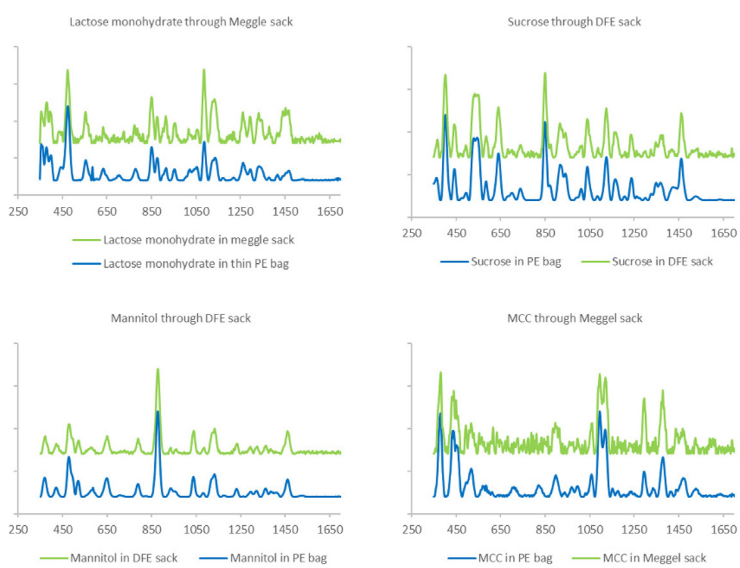



**Figure 2.** Sucrose and mannitol through a DFE sack, MCC and lactose monohydrate through a Meggle sack. SORS spectra overlaid with sucrose, mannitol, MCC, and lactose monohydrate Raman spectra through a polyethylene liner.

Table 2. Typical scan time for each raw material in Meggle and DFE paper sacks, with process hours in comparison to process hours by FTIR or conventional Raman

| Excipients | Typical Scan Time | Containers | Total Hours | Time Reduction Factor in Comparison with:* | |
|---|---|---|---|---|---|
| | | | | Conventional Raman Devices | FTIR in QC |
| Lactose monohydrate | 1 min 20 s | DFE bag | 4.4 | x 3.5 | x 10.7 |
| Lactose monohydrate | 1 min | Meggle bag | 3.3 | x 4.7 | x 14.3 |
| MCC | 1 min 20 s | DFE bag | 4.4 | x 3.5 | x 10.7 |
| MCC | 1 min 30 s | Meggle bag | 5.0 | x 3.1 | x 9.5 |
| Sucrose | 45 s | DFE bag | 2.5 | x 6.3 | x 19.0 |
| Sucrose | 30 s | Meggle bag | 1.7 | x 9.4 | x 28.5 |
| Mannitol | 40 s | DFE bag | 2.2 | x 7.1 | x 21.4 |
| Mannitol | 35 s | Meggle bag | 1.9 | x 8.1 | x 24.4 |

** Time reduction factor is calculated by assuming that total hours for the identification process are independent of which raw material is being measured with conventional Raman devices and FTIR. The total time for identifying lactose monohydrate (from Table 1) has been used as the basis for these calculations.*

## Conclusion

The Vaya Raman system can accelerate the receipt of raw materials by enabling identity verification through transparent and non-transparent containers in the quarantine area. By avoiding opening paper sacks, Vaya can reduce the time taken for receipt of large volume excipients to a matter of hours rather than days, reducing the cost of testing.

## References


1. EU GMP Annex 8: Sampling of Starting and Packaging Materials
2. Application of Spatially Offset Raman Spectroscopy to In-Container Testing of Raw Materials for PIC/S GMP Annex 8 Using the Agilent RapID Raman System, Agilent publication number 5991-8859.

Learn more:

**www.agilent.com/chem/raman-vaya**

Get answers to your technical questions and access resources in the Agilent Community:

**community.agilent.com**

U.S. and Canada

**1-800-227-9770**

**agilent_inquiries@agilent.com**

Europe

**info_agilent@agilent.com**

Asia Pacific

**inquiry_lsca@agilent.com**

DE44439.2567013889



Published in the USA, September 14, 2021
5994-4078EN

Agilent

Trusted Answers