

Photo courtesy of Sage Products LLC.

Raw material identification (RMID) is a crucial stage in the pharmaceutical manufacturing process and is essential for ensuring quality control and compliance with the latest industry regulations. A material intended for pharmaceutical products must be certified as fit for purpose. The RMID process is designed to ensure that the materials received from external suppliers are indeed the materials specified. Globalization of the pharmaceutical industry has led to the implementation of international standards. In fact, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-Operation Scheme now requires 100% inspection of raw materials in some countries, not including the U.S.

The RMID workflow traditionally involves material sampling of incoming batches which are then tested in on-site or off-site laboratories. However in the drive to achieve lean manufacturing processes, handheld Raman devices have been shown to optimize the RMID process and be as analytically effective as conventional lab-based methods.

Sage Products LLC, a manufacturer and distributor of health and personal care products for the hospital and retail markets, was looking to improve the efficiency of its manufacturing process by reducing the time and costs associated with RMID analysis which was being carried out by internal and external laboratories. Having implemented a 1064nm handheld Raman instrument from Rigaku Raman Technologies, Sage has benefited from the ability to analyze a wider range of raw materials in their on-site receiving warehouse, which has led to a 90% reduction in the cost of analysis per sample, and more importantly a reduction in testing turn-around times to minutes rather than days.

# Sage Products: The RMID Challenge

Founded in 1971, Sage's advanced patient hygiene products and programs are designed to help healthcare facilities improve clinical outcomes by reducing the risk of adverse hospital-acquired events including skin breakdown, pressure ulcers and surgical site infections. Sage's entire product line, which includes antiseptics and personal hygiene products, are manufactured at their state-of-the-art headquarters and production facility in Cary, Illinois. As a market leading manufacturer, Sage is focused on maximizing quality in its manufacturing processes to meet and exceed customer expectations. All of Sage's products are manufactured under current Good Manufacturing Practices (GMP) as required by the Food and Drug Administration (FDA). By integrating quality and regulatory compliance systems into all aspects of the product life cycle, Sage manufactures superior and reliable products that consistently meet high performance standards.



In order to ensure quality standards, Sage had implemented a rigorous inspection process for the testing of a wide range of natural, synthetic and solvent raw materials including liquids and powders. In line with FDA regulations, Sage was sampling and sending raw material specimens to either the internal or external laboratory for identification using a range of techniques. Any materials which were found to be incorrect by the identification test would be rejected by quality assurance and sent back to the vendor to investigate why the error had occurred. However, as the demand for Sage's products increased, the amount and variety of raw materials subsequently increased, proving the existing RMID process to be time consuming, inefficient, and very costly.

Deborah San Juan, QC Chemist at Sage Products who managed the implementation of the handheld Raman instrument described the process, "While analysis in our internal labs was taking between three to five days, it was taking anywhere between two to five weeks for results to come back from the external laboratory. This meant that we had to wait long periods of time before having the information required to enable us to make a decision about whether or not to accept or reject the materials for production. This was causing unnecessary delays in the production process." Quarantining materials waiting for clearance from the analysis also meant that a large portion of on-site floor space had to remain reserved for the holding of materials undergoing QC.

With such a large influx of materials, Sage was in need of a testing process that would be easy to introduce into its vertically implemented manufacturing process, while also saving time and money associated with external testing.

# **Capabilities of Handheld Raman for RMID**

Raman spectroscopy is a recognized technique in the U.S. Pharmacopeia (USP) for the testing and identification of materials. Through the collation of vibrational information specific to the bonds of the target material, Raman scattering is able to identify molecular 'fingerprints' to confirm the identity of the target material. For the purposes of RMID, Raman has been proven to be as reliable as lab-based testing methods and handheld Raman devices can perform quality control analysis on-site for much greater efficiency. A handheld Raman device by Rigaku Raman Technologies was selected by Sage Products to optimize its RMID process. Offering the ability to streamline manufacturing processes and save considerable time and resources, the implementation of a handheld Raman device represented a unique opportunity to increase productivity, improve efficiency and achieve cost savings while offering enhanced analysis.

The device selected by Sage was specifically designed for use in the warehouse for real-time, fast sample identification. By enabling analysis to be carried out at the point of need, the device delivers accurate identification and results in seconds rather than waiting for results from a laboratory. Equipped with a 1064nm excitation laser, the device enables QA Technicians the ability to increase the number of their identifiable materials. It was the capabilities delivered by the 1064nm laser that set Rigaku's handheld Raman apart from competitive devices explained Deborah, "Due to the aqueous nature (weak Raman scatter) and chemical properties of the samples, the ability to analyze these materials through borosilicate vials without issues of fluorescence interference and instability is a huge benefit. Unlike handheld Raman devices with 785nm or 532nm excitation lasers, the Rigaku device with the unique 1064nm laser could offer this broadened capability."

In addition, unlike most sample analysis techniques, the Raman device does not require sample preparation which saves further time in the RMID process. The fact that the testing is nondestructive adds to the desirability of the method.

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## **Implementation of Handheld Raman**

Sage referred to the USP and peer reviewed articles for best practice guidance on the implementation of Raman in the FDA-regulated GMP environment. A comprehensive Standard Operating Procedure was created for the device to ensure all the criteria for reliability (figures of merit), were met according to USP and ASTM standards. The qualification process, which involved tests to establish the suitability of the device for the specific needs of the QA technicians, took around three months to complete.

The key criterion for RMID is that the method being used is specific enough to accurately identify the compound being screened. During the testing process to validate the Raman method, Sage used qualified substances to prove the equivalence of Raman identification to reference methodology. Reference materials are typically authenticated in-house or are a USP reference standard. The acquisition of a reference spectrum is the single most important step in the development of a chemical identification as without an authentic reference system the validity of results may be questioned. The effectiveness of the Raman measurement was further demonstrated graphically through the use of a specificity matrix diagram of the various materials potentially received by Sage (Figure 1), which demonstrates the selectivity of their required qualitative chemical ID's.

	Methods/Hit Quality Indeces																				
Raw Materials	20% CHG Solution	Light Citrus Fragrance	Dissolvine GL-47s	MP Diol Glycol	Plantaren	Glycerin	Glyceryl-PEG 100 Stearates	70% Sorbitol	Propylene Glycol	Stearyl Alcohol	Propylparaben	Methylparaben	Arlamol E /Tegosoft	Citric Acid	Germall II	Polysorbate 20	Potassium Sorbate	Cetylpyridinium chloride	Decyl glucoside	Nonoxynol 9	Glucono delta- lactone
20% CHG Solution	95.3	6.5	0.0	0.2	4.4	5.6	7.6	6.6	2.1	3.0	37.3	41.8	4.7	6.5	2.5	7.5	0.3	0.5	5.3	7.8	0.1
Light Citrus Fragrance	7.0	90.0	2.5	42.8	19.5	14.8	24.2	2.4	25.0	21.6	10.8	7.2	37.5	0.7	0.2	46.3	0.9	28.9	14.1	65.9	2.5
Dissolvine GL-47s	0.0	1.5	97.4	0.1	12.6	0.2	3.7	1.1	1.2	13.4	0.1	0.7	12.4	14.6	0.3	2.2	0.8	0.5	9.7	0.8	0.0
MP Diol Glycol	0.0	18.2	0.4	91.2	10.1	35.5	17.5	3.2	56.3	5.9	0.1	0.1	31.5	0.4	0.5	58.3	1.0	9.3	10.9	70.0	0.0
Plantaren	2.9	11.1	10.8	15.8	95.1*	40.5	51.4	45.5	36.3	51.5	0.0	0.5	66.2	0.0	0.0	55.5	0.0	35.2	99.0 *	25.1	8.8
Glycerin	3.7	2.0	0.0	29.8	26.9	90.6	25.6	47.0	59.7	7.6	0.0	3.9	36.3	0.2	0.6	40.9	2.2	10.5	31.7	27.2	1.9
Glyceryl-PEG 100/ Stearates	4.0	27.8	5.5	34.7	58.7	36.7	94.1	20.8	32.9	68.1	0.7	5.8	66.7	0.2	0.4	80.7 **	0.0	45.2	52.2	50.7	1.8
70% Sorbitol	3.4	0.0	0.5	3.0	33.0	42.5	16.4	93.3	12.7	7.9	0.0	1.6	26.6	0.9	0.0	22.5	0.4	12.9	40.8	7.9	7.7
Propylene Glycol	0.8	7.9	0.2	49.1	22.2	49.9	19.5	10.2	92.9	5.2	0.4	0.9	44.2	0.4	0.1	51.8	1.0	3.6	25.4	38.3	3.0
Stearyl Alcohol	2.2	23.8	17.3	13.7	63.3	17.7	70.7	13.5	12.6	98.6	0.0	0.7	46.9	0.2	2.8	50.0	0.3	58.7	52.5	28.5	1.3
Propylparaben	51.9	21.0	0.2	0.0	0.0	0.0	1.1	0.0	0.3	0.0	99.2	65.3	1.1	3.1	3.6	1.2	5.4	0.0	0.0	3.2	2.1
Methylparaben	45.8	10.7	0.5	0.4	0.2	2.7	7.2	1.3	1.3	0.8	59.8	96.5	2.9	5.2	3.7	5.4	0.5	0.2	1.0	7.3	2.7
Arlamol E	3.5	24.5	11.4	35.5	64.1	47.3	54.8	34.5	48.6	37.7	0.5	3.1	96.1	0.3	0.0	69.8	0.4	24.8	60.2	56.8	0.5
Citric Acid	5.4	0.7	14.5	0.8	0.2	0.0	0.1	0.3	0.6	0.8	2.2	4.5	1.1	95.9	0.4	0.4	0.2	0.1	0.0	1.0	0.1
Germall II	1.7	0.4	0.3	0.3	0.0	1.1	0.0	0.0	0.4	1.3	1.3	1.9	0.3	0.7	80.8	1.3	0.3	6.8	0.5	0.5	0.1
Polysorbate 20	4.5	28.5	2.7	63.2	50.1	53.9	68.6	30.1	50.7	43.0	0.7	5.9	72.4	0.0	0.5	93.1	0.1	36.3	49.5	84.1**	0.1
Potassium Sorbate	1.3	4.6	3.5	1.0	0.2	2.3	0.2	0.4	0.9	0.6	5.0	1.2	0.0	0.0	0.6	0.0	99.6	0.4	0.1	0.0	0.8
Cetylpyridinium chloride	0.3	29.7	1.6	20.9	45.3	20.7	45.4	17.2	11.4	52.6	0.0	0.0	31.8	0.2	10.1	41.1	0.3	99.4	34.6	27.0	1.0
Decyl glucoside/Glucopon	2.1	12.4	11.5	17.0	96.3*	37.6	52.3	43.0	35.0	51.7	0.0	0.3	65.9	0.0	0.0	54.0	0.0	35.0	99.3*	24.6	9.2
Nonoxynol 9	5.0	47.6	1.1	72.6	28.9	37.4	51.7	11.4	43.5	33.2	3.4	6.3	58.2	0.8	0.0	81.7 **	0.1	32.1	32.2	99.0	0.3
Glucono delta-lactone	0.9	2.3	0.0	0.0	6.8	1.9	1.8	5.7	2.0	1.2	1.8	2.5	1.9	0.0	0.2	2.4	1.0	1.0	10.3	0.4	97.1



Figure 1: Sage's raw materials specificity matrix with raman analysis

\* Plantaren and glucopon are chemically known as decyl glucoside. Therefore, they both match each other when scanning with a Raman analyzer. Since glucopon and plantaten come from different vendors, additional ID method (pH) will be performed to distinguish one from the other.

\*\* Although polysorbate 20 has a high HQI (approximately 81) for glyceryI-PEG 100/ stearates and nanoxynol 9, the method is selective only for the polysorbate 20, which has the highest HQI.



Compliance with industry regulations was an important priority for Sage and a review of regulatory expectations was undertaken to ensure that FDA regulations 21 CFR Part 11, 210 and 211 and the EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines were met. Thanks to the ease of use and ergonomic design of the device the training process took just five days to complete and within a month, the process had been rolled out into full deployment.

Before deploying into the workplace, Sage set up different methods on the instrument for each material their technicians would be analyzing. When completing this process, they ensured that materials could be correctly identified with any method selected and still produce the correct results, delivering the levels of accuracy and reliability required within the application. This is clearly demonstrated in Figure 2, which shows butylparaben can be correctly identified by two different methods. Figure 3 shows that closely related materials – butylparaben, propylparaben and methylparaben – can be distinguished by Raman.

The results of the analysis demonstrated the ability of 1064nm handheld Raman to identify unique structural differences between propylparaben, methylparaben, or butylparaben and differentiate between one paraben and another. The unique peaks shown in the spectra also demonstrated the ability of Raman to fingerprint the unique properties of materials with similar structures. As a result, no second method would be required to confirm the identity of these raw materials.

Record Information:		Record Information:	
Device ID: \$1180011   User ID: dsanjuan   Test Time: 2014-01-29 16:10:24   Spectral ID: ID: 20140129160026   Method: R08411 Prosylparaben   Laser Power: 480 mW   Exposure Time: 400 mW   Average Number: 1   HOI Threshold: 30   HOI Window: 5   Search Range: 500 to 1800 cm^-1   Memo: Butyparaben 54830-50G-F tot BCBJ6690V   Matched Substance List: 1, Butyparaben (99.66, BS_User_Library.sdb)		Device ID: S1180011 User ID: dsnipan Test Time: 2014-01-29 16-21:39 Spectral ID: ID 2014012-816-21:34 Meltod: R084516 Meltyparaben Laser Wavelength: 1005 nm Laser Wavelength: 1005 nm Average Mumber: 1 HOI Threshold: 80 HOI Window: 5 Search Range: 500 to 1800 cm <sup>5</sup> 1 Meno: Butyparaben 54880-50G-F Library Used: 00: BS_User_Library.sdb Matched Substance List: 1, Butyparaben, (99.50, BS_User_Library.sdb)	
Export File Name:		Export File Name:	
ID_20140129160926		ID_20140129162124	
Back	Export	Back	Export

Figure 2: Identification: analysis of butylparaben with propylparaban method (left) and with methylparaben method (right). Butylparaben is correctly identified by each method.



Photo courtesy of Sage Products LLC.

Sage receives a wide range of raw materials that need to undergo testing. With such a large influx of materials, Sage was in need of a testing process that would be easy to introduce into its vertically implemented manufacturing process while also saving time and money.





Figure 3: Verification: analysis of butylparaben with propylparaben method (left) and then with methylparaben method (right). The methods shown will verify for a specific material, butylparaben, and so when closely related materials propylparaben or methylparaben are analyzed, the verification fails.

# Benefits of Handheld Raman for RMID

The handheld Raman instrument is now used for RMID in the incoming and receiving warehouse by QA technicians when raw materials are delivered at Sage. The instrument has enabled them to meet industry and their own internal requirements for RMID faster and more cost effectively than before. Sage has experienced an excellent return on investment following the implementation of Rigaku's handheld Raman device estimating that they have saved close to \$500,000 per year excluding overhead with the existing methods of analysis in place. Excluding capital and project expenses, that equates to savings per analysis greater than 90% of the original cost. Utilizing a cost benefit comparison, it took less than one year to reach the break-even point where savings exceeded the cost of implementation.

The use of the handheld Raman device has enabled QA technicians to screen samples on the spot and decide whether to release or reject materials within the same day of receipt, instead of having to wait three days minimum for internal lab results or several

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weeks for results from external laboratories. This has meant that testing cycles have been reduced from weeks to hours. Sage was able to dramatically reduce the cost of outsourcing RMID, free up QC lab resources and reduce quarantined material volumes. In addition, because technicians could spend significantly less time screening materials, they were then able to devote their expertise to other testing and development areas. One of the key features of the device was its secure software for 21 CRF Part 11 compliance helping Sage to easily meet required standards with electronic signatures removing the risk of human error.

Being able to test materials as they arrive at a manufacturing facility is extremely beneficial. In the time taken to prepare a single sample for laboratory testing, a handheld Raman device is capable of screening and verifying the identity of the material sample, completely eliminating lab-related delays and quarantine holding procedures. Even more importantly the 1064nm laser allows for samples to be measured through colored plastic containers protecting materials from contamination during the screening procedure.



Deborah explained "Due to the innovative nature of our work here at Sage, we are continuously adding new raw materials to our processes. Initially we were only working with four to five materials with the device but building the library on the instrument took less than a day to update. The fact that we can continue to add new materials to the library is a huge benefit and the device is now also being used to support new product development and product engineering projects aimed at establishing identification methods for the ingredients used in new products."

## **Revolutionized RMID**

Deborah summarized the impact the introduction of handheld Raman has had at Sage, "The integration of Rigaku's handheld Raman device into our RMID process has delivered a number of significant benefits. The significant reductions in analysis time have freed up valuable QC resources, not to mention costs associated with external laboratory analysis. The Rigaku handheld has proved easy to use while also providing superior performance thanks to the 1064nm excitation laser allowing us to overcome issues caused by fluorescence interference that affect other devices."

By introducing the new generation of handheld Raman from Rigaku into the RMID workflow, Sage has successfully achieved leaner manufacturing processes and lower costs per analysis without compromising on quality. For more information about the advanced handheld Raman instruments from Rigaku Raman Technologies visit www.rigakuraman.com or email sales@rigakuraman.com.



Photo courtesy of Sage Products LLC.

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### About Rigaku Raman Technologies

Rigaku Raman Technologies is leading with innovation to pioneer a portfolio of handheld and portable Raman products tailored to support the protection of public health and safety while aiding the advancement of scientific research and academic study.

To find out more about tailored Raman solutions with multiple laser excitation capability, please visit www.rigakuraman.com