VIAVI Solutions

White Paper

Raw Material Identification by NIR Spectroscopy

Raw Material Identification (RMID) is a first and fundamental step in a Quality by Design (QbD) process implementation. Ensuring that the material used in the manufacturing process conforms to the desired quality standard is essential to prevent potential failures in the finished product.

Introduction

Historically, RMID sampling criteria specified that the square root of the number of containers of both excipients and API were to be sampled. More recently, the European Pharmacopoeia raised the RMID requirements to 100% of material testing, and the volume of analysis performed in quality control laboratories became unsustainable. This regulatory change, now global, pushed instrument manufacturers to design "fit for purpose" solutions. In the early phase, many industries adopted NIR laboratory systems, redesigned for warehouse operation and equipped with fiber optic probes. Recently, the miniaturization of spectroscopy techniques such as Near-Infrared (NIR) and Raman spectroscopy have enabled portable, fit-for-purpose instruments that deliver an enhanced user experience, lower cost of ownership, and results as reliable as laboratory instruments.

Why RMID performed at the receiving point?

Receiving-point RMID is a critical step in QbD and LEAN implementations and allows manufacturers to:

- Significantly reduce the need for material quarantine, floor space, and sampling area
- Eliminate laboratory characterization and avoid material movement
- Dramatically reduce cycle time while increasing quality

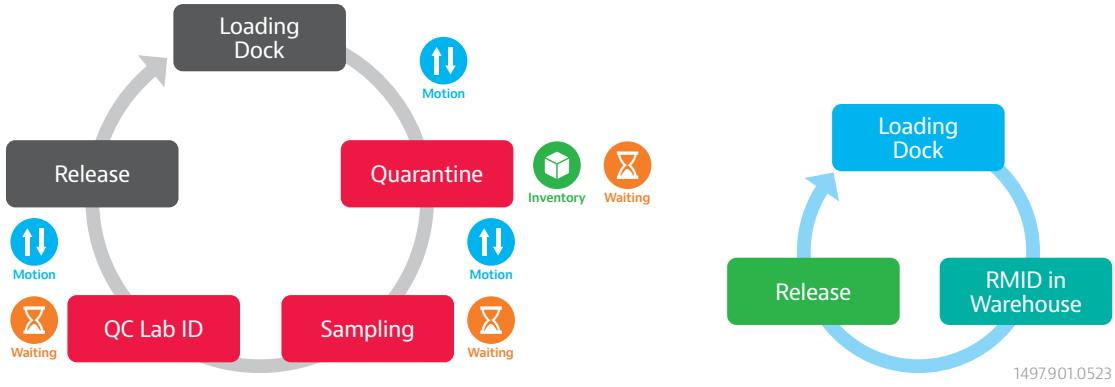

Fig. 1: Traditional RMID process cycle (left) compared to RMID performed in the manufacturing area wherein the cycle time can be minimized.

Several instruments are now available on the market for RMID purposes, primarily Raman and NIR handhelds. None by itself represents a total solution for the variety of materials and containers typically used in pharmaceutical, chemical, or food ingredients manufacturing sites. Most Raman systems are generally affected by fluorescence, a severe limitation that drastically reduces the number of measurable materials. Some Raman instruments reduce the limitation by using lasers with different excitation wavelengths, while others allow sampling through thick plastic containers. However, material identification by Raman spectroscopy alone is insufficient to qualify the material. Laboratory analyses such as loss on drying (LOD) and particle size measurements are still required. This why NIR and Raman are complementary in the RMID process as shown in Figure 2.

		Raman only		**Raman and NIR combined**	
Material	Container	Raman ID	QC Lab	Raman and NIR ID	QC Lab
API 1	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 2	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 3	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 4	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 5	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 6	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 7	Poly bag (LDPE 8 MIL)	Uncertain	Yes	Validated	n.a.
API 8	Poly bag (LDPE 8 MIL)	Uncertain	Yes	Validated	n.a.
Excipient 1	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 2	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 3	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 4	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 5	Poly bag (LDPE 8 MIL)	Uncertain	Yes	Validated	n.a.
Excipient 6	Poly bag (LDPE 8 MIL)	Fluorescence	Yes	Validated	n.a.
Excipient 7	Poly bag (LDPE 8 MIL)	Fluorescence	Yes	Validated	n.a.
Excipient 8	Poly bag (LDPE 8 MIL)	Fluorescence	Yes	Validated	n.a.
Excipient 9	Bottle light brown	Validated	n.a.	Validated	n.a.
Solvent 1	Bottle light brown	Validated	n.a.	Validated	n.a.
Solvent 2	Bottle light brown	Validated	n.a.	Validated	n.a.
Solvent 3	Bottle dark brown	Validated	n.a.	Validated	n.a.
Solvent 4	Bottle dark brown	Validated	n.a.	Validated	n.a.
Solvent 6	Bottle dark brown	Not measurable	Yes	Not measurable	Yes
Solvent 7	Bottle dark brown	Not measurable	Yes	Not measurable	Yes
Excipient 10	Bottle LDPE white	Not measurable	Yes	Not measurable	Yes

Fig. 2: In this RMID example, Raman is adequate to identify 15 of 24 samples, requiring 9 to go to the lab. Combining Raman and NIR expands the capability to 21 of 24, reducing the lab load to 3 samples. NIR also adds the ability to qualify materials for moisture and particle size, which Raman is unable to do.

When moisture content and particle size matter, identification by itself is insufficient to qualify the material for production.

Unlike Raman, NIR spectroscopy is very sensitive to moisture content and particle size, is not affected by fluorescence, and can qualify materials by characterizing multiple properties, as illustrated in Figure 3.

The VIAVI MicroNIR™ OnSite-W wireless NIR spectrometer embodies these advantages in a robust, compact, and repeatable handheld form factor ideally suited to the rigors of warehouse deployment.

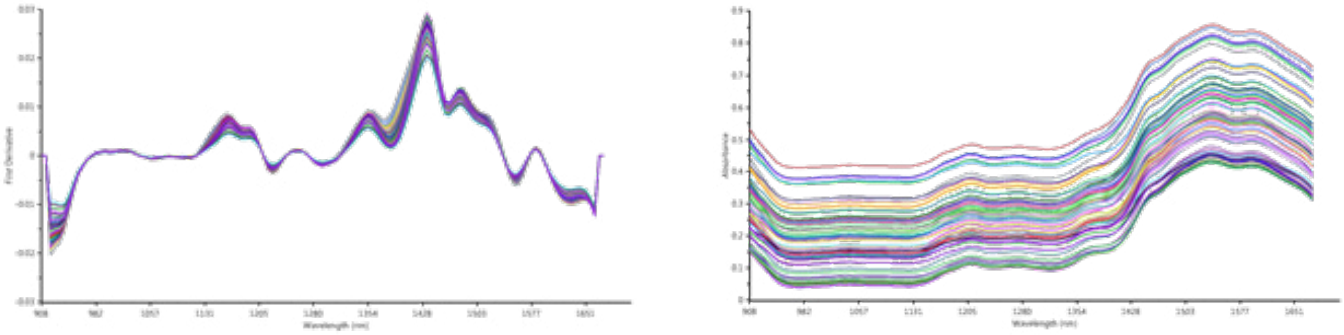

Fig. 3: Material composition, moisture, and particle size affect NIR spectra enabling material ID and qualification. **Left:** Preprocessed NIR spectra of moisture change in a drying process. **Right:** Raw data NIR spectra of particle size change in a high shear mixing process.

This document describes how to configure the MicroNIR OnSite-W NIR handheld for RMID.

The MicroNIR Pro software workflow allows multiple criteria of qualification, including the Spectral Match Values classification method to identify and the Partial Least Squares regression (PLS) method to quantify API concentration, moisture or particle size.

System Configuration and Results

Setting up the MicroNIR OnSite-W to perform material identification and qualification is fast and easy. The instrument does not require any setup; the essential preliminary work consists in the development of the materials library and, if necessary, the calibration models for other properties.

- Connect the instrument to the tablet PC or laptop via Bluetooth.
- Acquire spectra of reference materials
- Create the materials identification library and quantitative models for qualification
- Design the workflow and assign access to user
- Perform RMID on the floor

NIR measurements can be performed through plastic sacks to avoid possible contamination, exposure to atmosphere, and exposure of the operator to hazardous materials. The OnSite-W standard features and functions optimize accuracy, productivity, and ease of use. The included flat plate measurement collar ensures consistent sample presentation. A long-lasting battery (up to a week between recharges in typical use) yields high productivity. The instrument's light weight (8 oz./250 gr), ergonomic handle, single pushbutton operation, and rapid measurement cycle minimize operator fatigue (even with three repetitions, an operator can qualify a material in only a few seconds). Finally, by using a PC or tablet equipped with a bar code reader, the operator need perform no manual data entry, streamlining workflow and eliminating errors.

Fig. 4: The sampling collar, single push-button operation, rapid measurement cycle, and lightweight of the MicroNIR OnSite-W minimize sampling errors and fatigue. Results are displayed rapidly on the Bluetooth-connected tablet PC.

How to achieve highest confidence in the result: A real case study.

Several pharmaceutical materials were analyzed with the MicroNIR OnSite-W, using qualitative and quantitative chemometric models built in MicroNIR Pro software. The model library was developed by sampling six batches of each material. The collection time per batch was under 30 seconds in total, at default instrument data collection parameters. An additional set of data (1 batch of each material) was used to perform the library validation. The library included both excipients and APIs.

MicroNIR Pro software includes the powerful Spectral Match Value algorithm and library development routines designed to provide the highest degree of confidence in the results, including material-independent spectral pre-treatment and wavelength selection, as well as numerical and visual library validation and nearest neighbor ID option.

- Many materials have spectra that appear similar but can be easily distinguished by spectral preprocessing methods such as Standard Normal Variate (SNV) and first or second derivative smoothing. Materials of identical composition but different mesh size, on the other hand, are best distinguished at the level of unprocessed spectra (see Fig. 3). MicroNIR Pro has tools to address both cases.
- MicroNIR Pro calculates the correlation between the spectra of all materials in the library. Color coding is used to distinguish materials that can be distinguished vs. those that are ambiguous. The correlation threshold for each material is adjustable by the user. A high threshold may be used to screen out material with slightly different properties from the desired formulation.
- The nearest neighbor function identifies the library materials most similar to the sample tested for enhanced confidence in the uniqueness of the ID result.

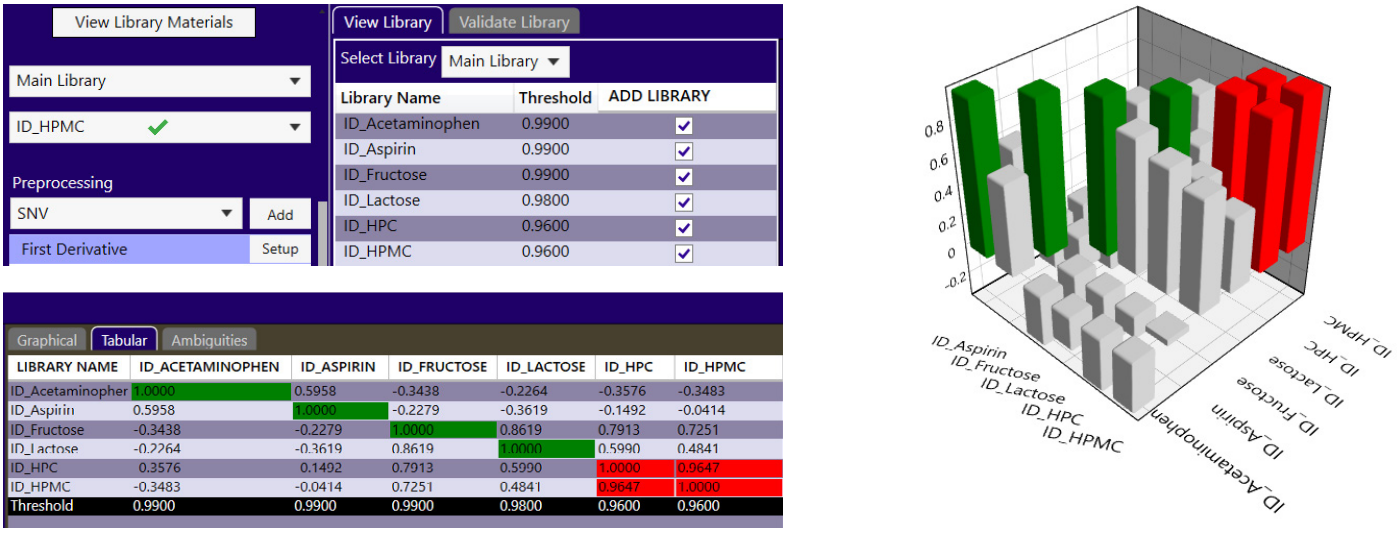

Fig. 5: A Spectral Match Value RMID library. The correlation between the mean spectra of each material is calculated and compared to the user-defined match threshold. The closeness of the match is shown by column height. Green and gray colors indicate that the material can be uniquely identified, red indicates ambiguities that should be resolved with a next-level classification step.

Advanced approach – combined qualitative and quantitative modeling

The ability of MicroNIR Pro software to apply multiple analytical criteria to the workflow allows the developer to combine qualitative and quantitative results. Qualitative (identification) criteria are developed using the SMV algorithm, or can also be imported from third party tools. Quantitative criteria – such as moisture and particle size – are developed from a PLS model built on samples characterized in a laboratory. Each of these samples can be named to include the relevant properties, for example "Avicel MCC PH200 PS 180 Moisture 2%" for the material with 180 micron particle size and 2% moisture. A model built this way will immediately tell the operator whether the incoming material passes or fails and what parameters are in or out of bounds. Clearly, once these methods are deployed on the loading dock, laboratory effort, reagent use, and cycle time can be dramatically reduced.

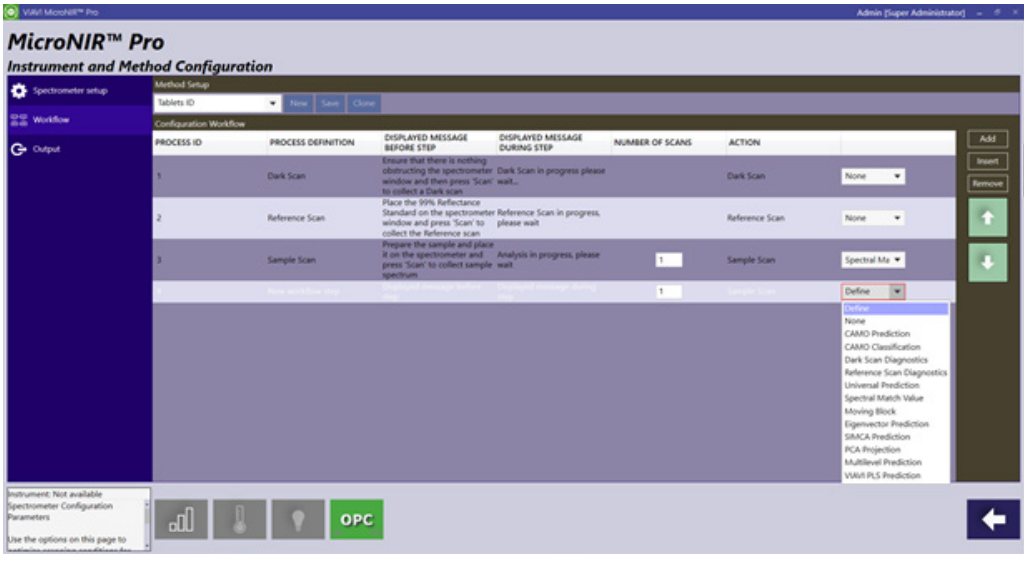

Fig. 6: The workflow of MicroNIR Pro software allows multiple data analysis steps. SMV can be used to identify the spectrum, while regression models can be added to quantify material concentration or specific property.

Conclusion

Material identification and qualification is an essential step of QbD and LEAN. 100% RMID has become established practice in the pharmaceutical industry and NIR is one of the best fit-for-purpose analytical techniques to perform such tasks. Unlike other technologies, NIR can identify materials and qualify them by multiple properties including moisture content and particle size, all while reducing workload on the quality control laboratory. The MicroNIR OnSite-W offers unique value to perform warehouse characterization of incoming materials, including:

- Identification and qualification of materials, including fluorescent materials that cannot be analyzed by Raman spectroscopy
- Confidence in the results by diagnostic tools and nearest neighbor ID scores
- Ease of use achieved by lightweight, single push-button operation and streamlined user interface
- Long lasting battery operation for uninterrupted work on the production floor

The MicroNIR OnSite-W can be used in place of LOD/titration for moisture content speciation, or to minimize the need for lab-based particle analysis. The industrial design is water- and dustproof (IP65/67) and its Bluetooth connectivity allows the use of tablet PCs which, if equipped with bar code reader, can also eliminate sample information typing errors. The MicroNIR OnSite-W can uniquely identify and qualify a wide variety of materials and represents an excellent solution for RMID, or a perfect complement to existing Raman-based processes.

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