Method Development and Validation: RMID for Regulated Industries

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Traditional time-consuming analytical techniques for Raw Material Identification and Verification (RMID) are being replaced by spectroscopic methods such as handheld Raman. In-situ RMID methods must accommodate new types of users, warehouse conditions, and faster sampling strategies without compromising the success of the method. This 4-part series guides Mira P users through method building, method validation and implementation.

Part IV discusses how RMID with Mira P can improve materials receiving and reduce the impacts of testing and quarantine on an operation.

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Metrohm Raman

Part IV – Method Implementation

In the pharmaceutical industry, warehouse verification of incoming materials with mobile Raman involves performing RMID directly at the loading dock. Chemical analyses that historically would be performed in a laboratory by trained chemists can now be performed, very quickly and with great success, by nontechnical professionals. Handheld Raman as an RMID technique has only recently achieved its full potential, due to advances in many fields. Below, we discuss the road to Raman in terms of regulations, compliance, and necessary safeguards for quality assurance.

RMID Part IV also illustrates several advantages that implementing a handheld Raman method for RMID can offer producers, in addition to specifics about Mira P and its unique workflows that support implementation.

Handheld Raman Grows Up

Over the past 20 years, Raman spectroscopy has evolved from a laboratory research tool to a companion for warehouse and field ID. This steady progress reflects great innovation resulting in sensitive, integrated, compact instruments that can analyze multiple sample types in various settings.

It also reflects development of the legal and scientific framework that supports industrial quality standards. These include:

- Reference standards: instrument standardization
- Instrument calibration routines: self-correction
- Library development: relevance to commercial samples
- Validation procedures: confirm instrument and method performance
- Data integrity: compliance, traceability, and records

Mira P is not merely a satisfying instrument in your hand. Consider the *incredibly broad picture painted above*. Mira P must also be a solution for materials verification that is **high-tech**, **smart**, **adaptive**, and **responsible**.

Advantages

Implementation of handheld Raman for RMID, where the majority of materials testing is performed in the receiving area, is a significant departure from classical methods. It has become widespread due to some very real advantages:

Substantial time savings
- Acquisition times of less than a minute, coupled with instant, clear results, allows very high throughput.

Reduced resources
- Less demand for laboratory and warehouse personnel and lab consumables, associated costs, and workloads.

Guided workflows
- Predefined workflows make sampling simple and efficient.

Faster turnaround
- Raw materials are delivered to production sooner.

Simplified materials handling
- Through-packaging and direct contact analyses mean no aliquots, no sample preparation, and no physical exposure.

No compromise on quality or compliance
- Maintain 100% testing on all received shipments versus spot checks.

Saving Time and Resources...

For raw materials inspection, a sampling rate of √(N)+1 has been deemed adequate for quality control since the 1920's. However, following quality control standards accepted by the FDA's Current Good Manufacturing Practices (cGMP in CFR) [1], there has been a more recent shift toward 100% testing by food, pharma, and nutraceutical producers. In this demanding arena, handheld Raman is especially effective.

In classic RMID, each received container is opened, sampled, and quarantined until each sample has been confirmed with analytical laboratory techniques such as ATR (Attenuated Total Reflection), GC/MS or HPLC.

In an ideal scenario, where containers are sampled and tested immediately upon receipt, RMID for 100 containers requires **more than 14 hours** before release to production.

The resources required for 100% laboratory testing are considerable:

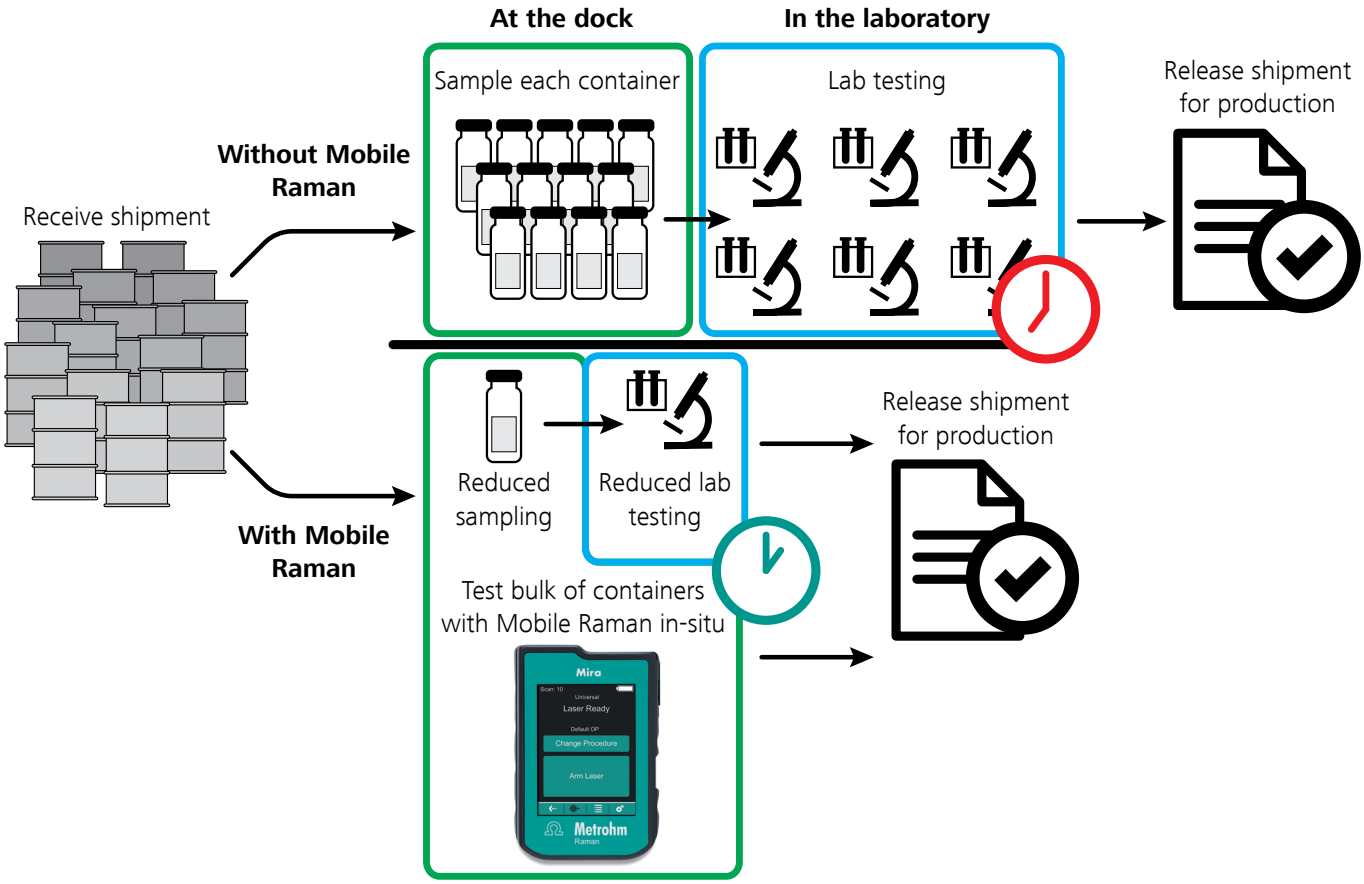
- Collecting sample aliquots is both labor- and time-intensive.
- Analytical lab techniques require experienced personnel.
- From sample vials to solvents to instruments, collateral material costs are considerable.
- Lab backlogs dictate testing and release schedules.

...With Mira P

RMID with Mira P avoids the majority of issues involved with aliquot collection, testing expertise, and use of laboratory resources.

In this scenario, √(N)+1 samples (11 out of 100) are fully tested in the lab, while the remainder are tested at the receiving dock. With Mira P, the remaining 89 containers can easily be sampled within 2 hours, and the reduced workload then leads to a faster turnaround for lab samples. The time estimate for 100% testing of 100 containers is **less than 4 hours**.

The math is easy: a reduction of approximately one hour of extra work per 10 containers using Mira P for RMID versus 100% laboratory testing. Over the course of a year, the savings is startling.



Method Development

RMID Parts I, II, and III describe method development in detail.

It must be emphasized that method development is performed by a laboratory manager. This is a professional who is knowledgeable about relevant chemicals and RMID analyses, *and* who is also familiar with warehouse routines and personnel. The lab manager is responsible for developing a method that:

- is relevant to local materials in terms of their nature, composition, and packaging
- conforms to established standards
- is robust
- can be achieved by target individuals

Both the method administrator and the routine tester must take steps to ensure that a method is both appropriate and properly implemented.

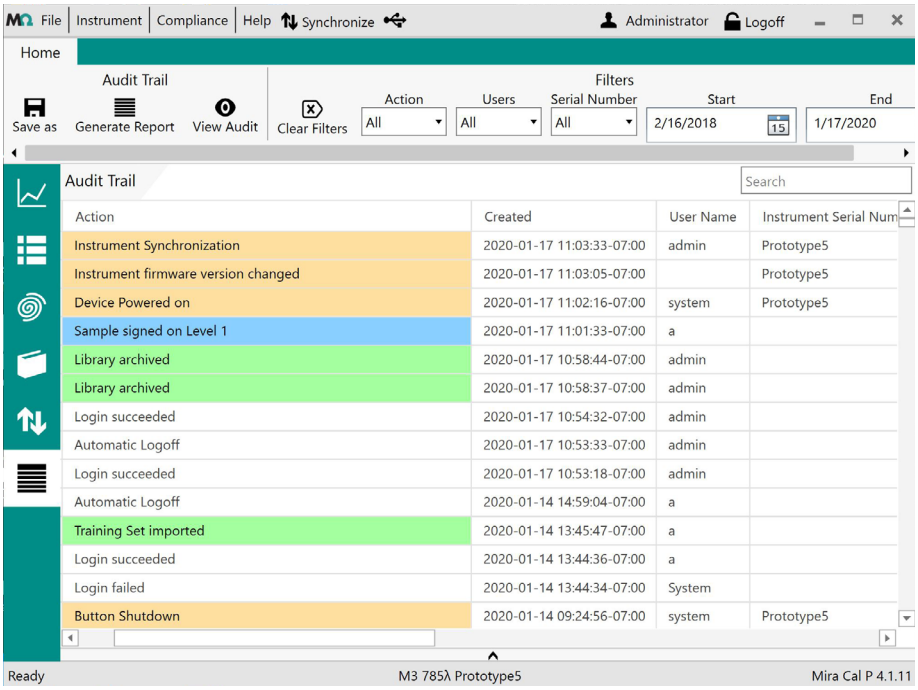
Information Security and Fidelity

Mira P contains a suite of features that support method development in terms of user access, data integrity, and records. [2–4] After the lab manager finalizes a method, he or she can sign it. Once the method is signed, both the system and software are accessible to authorized personnel only.
Mira P utilizes predefined user levels:

- **Administrators** can manage user access.
- **Lab managers** can create and validate different material methods and libraries, as well as print and sign reports.
- **Routine Users** can only log in and acquire data through pre-defined workflows.

Each user is assigned a unique username/password combination that cannot be duplicated. Each of these features ensures that a method can *only be used as intended*.

Mira P employs **audit trails** to log every action that is performed on the instrument, or with software while used in standalone mode or connected to the software. Audit trails are transferred from instrument to software upon each synchronization and, importantly, cannot be changed. An accurate record of all actions is stored in a secure database.



Example of an audit trail on Mira P.

Method Implementation

Mira P provides a predefined workflow for testers. Once the method has been transferred to the instrument, implementation is simple.

Step 1. The predetermined operating procedure (OP) for a material is selected by barcode reader or touch screen.

Step 2. If this is not specified in the OP and completed automatically in Step 1, container identifiers should be entered by barcode reader or touchscreen.

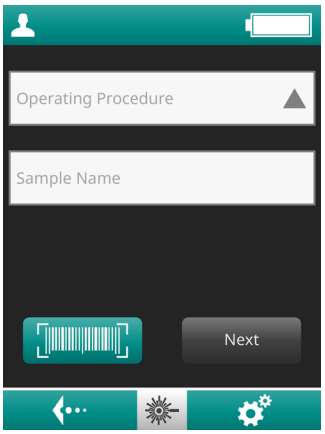
Step 3. Initial data is entered, and Mira P is ready to make a measurement.

Step 4. Proper laser safety states that the laser must be «armed» as a preliminary step to laser activation.

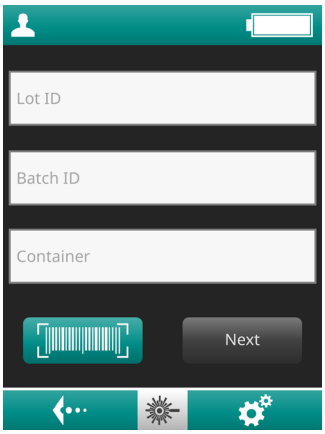
Step 5. Mira P acquires a Raman spectrum using the preset parameters defined the selected OP.

Step 6. Automated on-device routines process the result and return a decision supported by a p-value. Red or green screens provide quick visual confirmation of results.

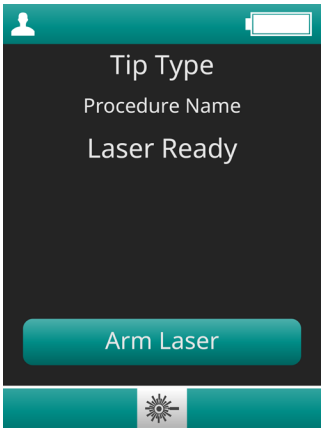
All relevant test and result data is automatically stored on Mira P, to be downloaded to Mira P Cal upon the next synchronization.



Step 1



Step 2



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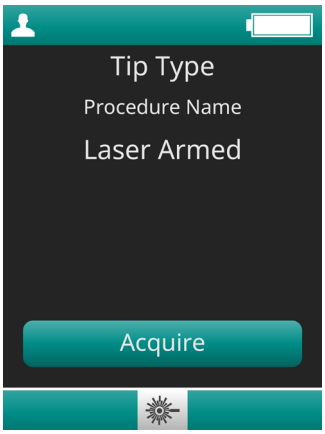
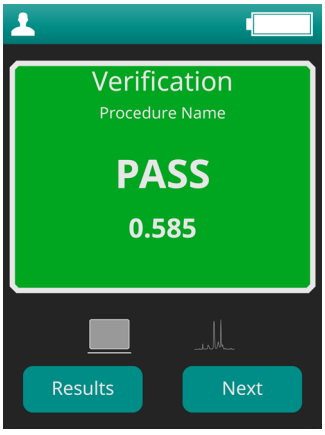


Step 4

Step 5



Step 6

Conclusion

Mira P can streamline receiving and release processes while maintaining high quality standards. This document is intended to address suitability of handheld Raman as a raw material identification method, and to describe the best practices for building RMID methods, in addition to step-by-step instructions outlining model building and validation. Details of compliance, implementation, and actual instrument use are included for the convenience of Mira P users.

References

[1] US FDA Title 21 Code of Federal Regulations, 21 CFR Part 11: Electronic records; electronic signatures.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11

[2] US FDA Title 21 Code of Federal Regulations, 21 CFR Part 211. Current Good Manufacturing Practice for Finished Pharmaceuticals
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211

[3] Metrohm White Paper- 038EN FDA 21 CFR Part 11 Compliance by Metrohm Raman
https://www.metrohm.com/en/applications/WP-038EN

[4] Peace of mind with Mira Cal P – Compliance with the Data Integrity Guidelines Made Easy
https://www.metrohm.com/en/documents/80005280

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