Inspection of raw materials and chemicals by using Raman Spectroscopy

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Industry Trends and Requirements

Incremental Regulatory Control for Incoming Material Identification. Regulated markets (pharma, vet, nutr...)
- PIC/S recommendations on complete traceability of incoming materials
- GMP is expanding to new products

Global Supply Chain
- Companies are moving toward a more delocalized supply chain
- Problems associated with supplier quality assurance and transportation

Quality Assurance and Cost Reduction
- Increase analytical capabilities
- Reduce operational cost
- Optimize operational efficiencies
Ideal Requirements (5S+C Rules):

Sensitive – capable of detection of deviations
Selective – many peaks/bands, minimal outside interference
Simple – used by spectroscopists and non-specialist operators
Stable – results must be homogenous through samples, time or environment
Specific – designed for or customizable to target environment

And….Cheap to implement!
Technology can help
Spectroscopy
Raman
What is Raman Spectroscopy?

- Molecular spectroscopy that can be used to provide a “fingerprint” of a compound based on the chemical bonds.
- Based on inelastically scattered light from a molecule.
- Not for trace level detection (~ <1%).

Advantages:
- Can perform analysis directly through transparent containers.
- Samples can be solids, liquid, slurries.
- Applicable for both qualitative and quantitative analysis.
- Little to no sample preparation required.
- Insensitive to aqueous absorption bands.
- Doesn’t require large sample volume.
- Highly selective.
- Fast analysis times.
**History of Portable Raman**

1928: Effect is discovered by C.V. Raman

1960: Laser is invented, stimulates a new wave of interest in Raman

1986: First FT-Raman

1995: Rapid technological advances make miniaturization of Raman possible

2000: Introduction of first handheld Raman spectrometer

2003: B&W Tek deploys approximately 10,000 Raman units, nearly doubling total deployment of Raman spectrometers worldwide

2005: B&W Tek introduces the NanoRam handheld Raman spectrometer (targeted at the pharmaceutical industry)

2006: B&W Tek introduces their first portable Raman spectrometer (targeted at nutraceuticals)

2011:
What Are companies and Gov. institutions Looking For?

- Compliance with company production and profitability targets
- Compliance with regulations
- Optimization of resources
- Team development and productivity
- Simplification of operating procedures
- Full operations traceability
- Safety and security

Before introducing handheld Raman in incoming materials at the warehouse

After introducing handheld Raman
Raman Spectra

Raman Shift
- Independent of laser output
- Excitation wavelength is determined by analytical and sample needs (avoid fluorescence interference with longer wavelength)

Raman Intensity
- Depends on laser wavelength
- The longer the excitation wavelength the lower Raman peak counts (at same power output)
Towards 100% Material Inspection

Why do we benefits of Identity Testing?

But, keep in mind, Raman isn’t magic, and it has its limitations!
Benefits of Handheld Raman for ID

- Reduced material movement – directly implement in warehouse, loading dock
- Easy and simple operations - simple training & improved resource usage
- Reduce chemical exposure – scan through packaging materials & maximize personnel safety
- Fewer lab delays reduce cycle time – on-time production & higher throughput; reduce material quarantine time and stocks
- Free up laboratory resources – increases lab capacity
- Reduced transcription – fewer errors; lower personnel and equipment overhead; control costs
NanoRam Handheld Innovations

- Only handheld with high resolution touch screen interface
- Only handheld offering easy data management and reporting
- Best methodologies for robust analysis
- Fastest in adding Methods and Libraries
- Only handheld allowing editing Method
- Full method development and validation support
Issues and Customer Concerns

• Can Raman help my project?
• What are the differences between Raman and other spectroscopy techniques like NIR?
• Should I really perform 100% container ID test? What are my options?
• Do I need to validate the Raman method? If yes, what are the requirements for method validation?
• What is next after the Raman ID becomes a routine method?
• Do I need to know the filing expectations from regulatory agencies, do they apply to me? (JP/EMA/FDA..)
• Can vendors provide GMP support & related documents?
Raman can measure through packaging: broad class

<table>
<thead>
<tr>
<th>Bottles</th>
<th>Manufacturer</th>
<th>Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amber Glass</td>
<td>VWR</td>
<td>3 mm</td>
</tr>
<tr>
<td>Clear Glass (A)</td>
<td>I-Chem</td>
<td>2 mm</td>
</tr>
<tr>
<td>Clear Glass (B)</td>
<td>VWR</td>
<td>2 mm</td>
</tr>
<tr>
<td>High Density Polyethylene (HDPE)</td>
<td>VWR</td>
<td>1 mm</td>
</tr>
<tr>
<td>Teflon FEP</td>
<td>Nalgene</td>
<td>1 mm</td>
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<tr>
<td>Polystyrene</td>
<td>Uline</td>
<td>1 mm</td>
</tr>
<tr>
<td>Vials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amber Glass</td>
<td>Kimball</td>
<td>1 mm</td>
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<tr>
<td>Clear Glass</td>
<td>Kimball</td>
<td>1 mm</td>
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<tr>
<td>Bags</td>
<td></td>
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</tr>
<tr>
<td>Polypropylene (PP)</td>
<td>Uline</td>
<td>2 mil</td>
</tr>
<tr>
<td>Low-Density Polyethylene (LDPE)</td>
<td>VWR</td>
<td>2 mil</td>
</tr>
</tbody>
</table>
Some Raman Applications In Use TODAY

• **ID**
  – Identification of raw materials (building up an extensive library of Raman spectra); *This is the application for NanoRam*

• **Quantitative analysis (**i**Raman products)**
  – Quantitative determination of substances in different formulations;

• **Polymorphism (**i**Raman products)**
  – Supporting polymorphic screenings (polymorphs have different solubility rates, thereby impacting the effective dosing);

• **Process (PAT) (**i**Raman and MiniRam products)**
  – Supporting chemical development process scale-up (as process steps are modified and refined to ascertain whether the desired chemical is being produced or not, and the rate at which it is formed).

• **Identification of unknowns (**i**Raman and nanoram)**
  – Forensics, military, police, art conservation

• **Material characterization (**i**Raman products)**
  – Define characteristics of materials
  – Unique fingerprint
Portable Raman Instruments

Units in each market are designed with key features and characteristics to address specific needs within the market.

Some common considerations are:

- High resolution requires a larger footprint
- Handheld instruments require fast on-board analysis
- Portable instruments require highly flexible sampling capabilities
The Measurement Challenges - Measure Through Plastic Packaging

Implementation advantages of spectroscopic methods
- No cross-contamination (the material inside the bag)
- Safe and easy to implement
- Can be implemented in warehouse, docking area or lab

But...Challenges exist if using e.g. NIR technique
- Spectral profiles include packaging absorptions
- Packaging interferences may reduce the specificity of the method when identify similar materials
- The library requires assessment or change if the bag changes, i.e., not suitable for multiple suppliers of same materials
- Packaging could have multiple layers, with different colors or materials
NIR Spectra of caffeine (Plastic bag contribution)

NIR Spectra of material – with plastic bag

One layer PE bag

Two layer PE bag

No PE bag (pure sample)

Required to evaluate the method specificity in the presence of bag!
Raman Spectra of caffeine (Plastic bag effect)

No significant spectral absorption from PE bag
Raman has greater specificity than NIR
Spectroscopic-based Identity Method

- Sample analysis
  
1. Access Method
2. Scan sample
3. Identify Material

Operators
Tools for different verification modes of materials.

- Identification vs. defined method with p-value (significance level)
- Investigation for unknown samples: HQI

- In general, we recommend the use of p-value for ID (identification mode).
- The HQI (Investigation mode) may be considered an additional tool for validation.
Investigation vs identification on the nanoram

Uses statistics, it is used for example to verify that paracetamol is paracetamol, independently of the supplier, container or grades. That variation must be included in the population of the method.

Uses HQI to recognize which e.g. supplier of paracetamol is. Here each supplier, container or grade may have a different signature. Requires to setup the libraries.
Validation and/or identification by correlation with a reference, HQI results: from 0% (no relation) to 100% (perfect match)
What HQI means?

HQI is the spectral correlation coefficient, i.e. a normalized measure of spectral covariance

\[
HQI = \frac{(\text{Library} \cdot \text{Unknown})^2}{(\text{Library} \cdot \text{Library})(\text{Unknown} \cdot \text{Unknown})}
\]

Nobel prices/country/population vs. amount of chocolate/person. Correlation **does not** imply causation.
When running IDENTIFICATION and fails, I have some potential hits, what is this?

If an identification fails, the system will automatically run an investigation of potential matches.
Spectroscopic-based Identity Test

- The methods/libraries must be developed and can then be run on routine basis

- Method development
  - Well-trained analysts

1. Measure 3-10 Batches; NanoRam uses 20 spectra
2. Threshold p-value 0.05 based on PCA of 20 spectra
3. Build & Test Method
Powerful Spectroscopy!!!

Capable to differentiate the smallest changes!!!

HQI 100% correlation

HQI 99% correlation

Reference in library: Calcium Stearate
Samples were analyzed on glass vials to reduce container interference. The system is powerful enough to identify the small differences on the structure introduced by the counter ion.

100% correlation with reference on library

99% correlation with reference on library
**Best-of-kind Data reproducibility**

<table>
<thead>
<tr>
<th>Unit A</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Manitol</td>
<td>PVC</td>
</tr>
<tr>
<td>Repetition1</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>Repetition2</td>
<td>99</td>
<td>97</td>
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<td>Repetition3</td>
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<td>97</td>
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<td>Repetition4</td>
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<td>97</td>
</tr>
<tr>
<td>Repetition5</td>
<td>99</td>
<td>97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unit B</th>
<th>Glutamic acid</th>
<th>L-Alanyl-L-Glutamine</th>
<th>Tryptophan</th>
<th>Threonine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition1</td>
<td>99</td>
<td>99</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Repetition2</td>
<td>99</td>
<td>100</td>
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<td>96</td>
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<tr>
<td>Repetition3</td>
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<td>100</td>
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<td>97</td>
</tr>
<tr>
<td>Repetition4</td>
<td>99</td>
<td>100</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>Repetition5</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>98</td>
</tr>
</tbody>
</table>

Level of HQI can be increased to 100% adjusting the acquisition parameters.
Best-of-kind Data reproducibility

<table>
<thead>
<tr>
<th>Unit C</th>
<th>Olive Oil (search range 175-2500)</th>
<th>Olive Oil (search range 175-1900)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition1</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Repetition2</td>
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<td>100</td>
</tr>
<tr>
<td>Repetition3</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Repetition4</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Repetition5</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>
**Proximity Matrix**

Proximity Matrix: Testing of all the materials in Identification Mode using specific methods generated by each of the reference materials.

<table>
<thead>
<tr>
<th>Method Materials</th>
<th>Method A</th>
<th>Method B</th>
<th>Method C</th>
<th>Method D</th>
<th>Method E</th>
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</thead>
<tbody>
<tr>
<td>Material A</td>
<td>PASS</td>
<td>Fail</td>
<td>Fail</td>
<td>Fail</td>
<td>Fail</td>
</tr>
<tr>
<td>Material B</td>
<td>Fail</td>
<td>PASS</td>
<td>Fail</td>
<td>Fail</td>
<td>Fail</td>
</tr>
<tr>
<td>Material C</td>
<td>Fail</td>
<td>Fail</td>
<td>PASS</td>
<td>Fail</td>
<td>Fail</td>
</tr>
<tr>
<td>Material D</td>
<td>Fail</td>
<td>Fail</td>
<td>Fail</td>
<td>PASS</td>
<td>Fail</td>
</tr>
<tr>
<td>Material E</td>
<td>Fail</td>
<td>Fail</td>
<td>Fail</td>
<td>Fail</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Provides an overview to illustrate which chemicals may produce:
- False Positive
- False Negative
- good signal
- bad signal...

- p-value $> 0.05$
- p-value $0.001 < 0.05$
- p-value $10^{-6} - < 10^{-3}$
- p-value $10^{-15} - < 10^{-6}$
- p-value zero
Common Questions from Customers…….
Q1: What is the difference between ID and purity tests

“Identity” and “Purity” are two separate specifications.

- “Purity” implies some type of quantitative method; typically HPLC
- “Purity” is a test for specific impurities such as low level contaminants/adulterants.
- An identity test says nothing about purity, strength, or composition.
  - Usually gives “binary result”: Positive/Negative; Pass/Fail; Yes/No
  - Identity verifies it is similar to what has been used in the past

Every proposed method should be validated if it is used for quality decision!
Q2: How long does it take to get a Raman Method in place

• Bottleneck:
  – Document preparation & internal review
  – Assembling samples

• Example: Develop an ID method for 10 materials:
  – Training < 1 week
  – Method development 1-2 weeks
  – Specificity & robustness tests < 1 week
  – Documentation (prepare, review & approve) 2-4 weeks

• The first ID method validation takes 4 - 6 weeks
• The next ID validation project takes only 1-2 weeks

B&W Tek can provide Support Services
Q3: How do traditional vs. spectroscopic-based methods compare?

• In traditional methods often have a univariate calibration model
• Spectroscopic method based on chemometric modeling or statistical calculations
  – Identification/Qualitative
    • Calculate spectral similarity between method and unknown samples
    • Specificity test- interval validation evaluation focus on the model correctness of spectral library

Note: Different terminology:
Calibration in chemometrics- method/model calibration
Calibration in GMP environment - e.g., instrument calibration
Raman has proven to be a promising tool to increase operational capabilities and reduce cost.
THANK YOU FOR YOUR ATTENTION

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BACK UP SLIDES
Raman Related Documents (2)


- US FDA Advancing Regulatory Science at FDA: A Strategic Plan (August 2011): Section 2. Develop new analytical methods:
  a) Investigate feasibility and value of using emerging and improved analytical technologies like Nuclear Magnetic Resonance (NMR), mass spectrometry, or near infrared or Raman spectroscopy for evaluating product quality of pharmaceutical agents, and evaluate whether these technologies should replace existing methods;
## USP <1225> Validation of Compendial Procedures

<table>
<thead>
<tr>
<th>Analytical performance characteristics</th>
<th>Category I</th>
<th>Category II</th>
<th>Category III</th>
<th>Category IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quantitative</td>
<td>Limit tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>Yes</td>
<td>Yes</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Precision</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Specificity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>*</td>
</tr>
<tr>
<td>Detection Limit</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>*</td>
</tr>
<tr>
<td>Quantitation Limit</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>*</td>
</tr>
<tr>
<td>Linearity</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>*</td>
</tr>
<tr>
<td>Range</td>
<td>Yes</td>
<td>Yes</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*It may be required, depending on the nature of the specific test.*
Regulatory Standards Compliance

- 21 CFR Part 11 Electronic Records; Electronic Signatures
- 21 CFR Part 1040.10 Laser and Laser Systems
- US Pharmacopeia <1120> Raman Spectroscopy
- European Pharmacopeia Ch.2.2.48 guidelines for Raman Spectroscopy
Why do Raman ID methods fail? (1)

- Failure to include lot-to-lot variability
  - use numerous non-consecutive lots
  - realize material potential variability (particle size, moisture, mechanics etc.)

- Failure to understand the limitation of Raman
  - fluorescence interference
  - low Raman scattering signal (e.g., cellulose, salts, metals)
  - low concentration (e.g., tablet API)

- Potentially close materials give ambiguous results (pass more than one method)
  - Adjust p-value to narrow acceptance range for material, and limit overlap of methods
Why do Raman ID methods fail? (2)

• Occasional operational errors
  • Sampling/scanning problem
  • Quality of sample vials (sealed, glass etc.), plastic bags or containers
  • Method specific to particular sampling accessory and/or packaging
• Limited knowledge or misuse of identity algorithms
  • Performance/sensitivity of identification method (p-value is based on a PCA model on the 20 scans in the method)
Deficiencies of Filed Spectroscopic Methods (1)

• Absence of instrument description
  – Light source, design, detector, sampling module, software package
• Minimal description of chemometric techniques
  – Algorithms for pass/fail results
  – Method validation
• Limited results for method validation
  – Without acceptance criteria (ID thresholds)
  – Detailed results (with predicted values, not just pass or fail)
  – Inappropriate selection of negative control samples (material structurally similar or closely related to the analyte)
Deficiencies of Filed Spectroscopic Methods (2)

• Inadequate SOPs and plan for change control
  – Spectroscopic method performance verification?
  – Spectroscopic method maintenance plan?

• Lack of information for library/method update plan
  – SOPs for method/library update?
Raman Method Development

• Raman bands are distinct and can be easily related to chemical structure - very good for fingerprinting.

• Conduct a feasibility test:
  – To ensure sufficient sensitivity for compounds to be included in the reference library (very weak scatterers)
  – Minimize fluorescence interference/impurities
  – Laser powers and exposure times
    • confirm that the sample is not being altered
  – Sampling
    • Appropriate sample accessory

• Collect valid representative samples
  – Understand the sources of variations
    • Glass vial and packaging materials’ variability
    • Material lot-to-lot variability
    • Supplier variations
  – Need to evaluate the performance on testing numerous lots of material
Raman Method Development

- Raman bands are distinct and can be easily related to chemical structure - very good for fingerprinting.

- Raman spectral data collection
  - Measure through containers and plastic bags with appropriate accessory; contribution from the packaging components are usually very minor
  - System automatically determines scan time to give sufficient Raman signal for each sample
  - Collect 20 scans for each method – best to use different lots

- Identification Method
  - The method is based on the 20 scans of the material
  - A multivariate model of the spectra (PCA) with Hotelling’s $T^2$ limit determined (95% confidence; $p = 0.05$)
  - $p$-value used as Pass/Fail criterion
Validation

- **Process** of providing **documented evidence** that something does what it is **intended to do**
- Process, system, method

Qualification

- Inspection, testing and documentation review
- Is a part of the validation process which verifies module and system performance prior to being placed in routine use
- Equipment/instrument
Analytical Method Development

Prerequisites for analytical method validation—Six “M”s

- **Man**: qualified skilled
- **Machine**: calibrated qualified robust
- **Methods**: characterized documented suitable
- **Material**: Qualified Material Quality
- **Milieu**: Vibrations Temperature Humidity Irradiation Time Supplies Analysts’ support
- **Management**: Quality of the analytical method
# Analytical Instrument Qualification

**Table 1. Timing, Applicability, and Activities for Each Phase of Analytical Instrument Qualification**

<table>
<thead>
<tr>
<th>Design Qualification</th>
<th>Installation Qualification</th>
<th>Operational Qualification</th>
<th>Performance Qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing and Applicability</strong></td>
<td></td>
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<tr>
<td>Prior to purchase of a new model of instrument</td>
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<tr>
<td>At installation of each instrument (new, old, or existing unqualified)</td>
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<tr>
<td>After installation or major repair of each instrument</td>
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</tr>
<tr>
<td>Periodically at specified intervals for each instrument</td>
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<tr>
<td><strong>Activities</strong></td>
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<tr>
<td>Assurance of manufacturer’s DQ</td>
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<tr>
<td>Description</td>
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<tr>
<td>Fixed parameters</td>
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<tr>
<td>Preventive maintenance and repairs</td>
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<tr>
<td>Assurance of adequate support availability from manufacturer</td>
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<tr>
<td>Instrument delivery</td>
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<tr>
<td>Establish practices to address operation, calibration, maintenance, and change control</td>
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<tr>
<td>Instrument’s fitness for use in laboratory</td>
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<tr>
<td>Utilities/facility</td>
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<tr>
<td>Assembly and installation</td>
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<tr>
<td>Network and data storage</td>
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<tr>
<td>Secure data storage, backup, and archive</td>
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<tr>
<td>Installation verification</td>
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<tr>
<td>Instrument function tests</td>
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<tr>
<td>Performance checks</td>
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</table>
DQ/IQ/OQ and PQ Documents for NanoRam
Calibration Validation: part of the PQ

Self check: by performing calibration validation using ASTM 1840 ref material: Polystyrene
Method Development- Special Considerations for Raman Technique

- Fluorescence interference/presence of impurities
  - Baseline shifts and background signal
- Laser power
  - Confirm that the sample is not being altered. We keep information on laser power in the method.
- Sample-position sensitivity
- Use of appropriate sampling accessory.
NanoRam: Operation Preset

- Managerial level access to set Operation Preset

- ADMIN can also
  - create user accounts: Developer and Operator level users
  - Create calibration files
Selecting libraries to use in Investigation

• The libraries against which the search and match is performed can be modified.

• Multiple libraries can be selected.

• The Methods also can be searched to establish a match of materials using an HQI against every Method.
# NanoRam User Levels

<table>
<thead>
<tr>
<th>User Type</th>
<th>User Type Symbol</th>
<th>User Privileges</th>
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<tbody>
<tr>
<td>Operator</td>
<td></td>
<td>Select Method</td>
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<td>Perform Material Identification</td>
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<td>Select Operation Preset</td>
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<td>Developer</td>
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<td><em>All above, plus:</em></td>
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<td>Create/Modify Operation Preset</td>
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<td>Create/Modify Data Library</td>
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<tr>
<td>Administrator</td>
<td></td>
<td><em>All above, plus:</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manage User Accounts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Create calibration files</td>
</tr>
<tr>
<td>Device Manager</td>
<td></td>
<td>Set system clock</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Set password expiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Create calibration file</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reset ADMIN password</td>
</tr>
</tbody>
</table>

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User accounts

- ADMIN user can create other accounts
- Three levels of users:
  - Operator
  - Developer
  - Administrator
Analytical Method Validation

Do we need to perform method validation of spectroscopic-based techniques?