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Thermo Scientific TruScan RM

United States Pharmacopeia (USP)
Chapter <1120> — Raman Spectroscopy
Statement of Compliance

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2016 Update

The United States Pharmacopeia general chapter <1120>[1] Raman Spectroscopy provides an informative introduction to the Raman effect, followed by general technical guidance. Raman has extremely broad applicability in pharmaceutical manufacturing and R&D, from in-line process monitoring to polymorph screening with Raman microspectroscopy to incoming raw material identity testing. Therefore, not all elements of USP <1120> are relevant for qualitative analysis, especially the elements related to identity testing. Furthermore, the general chapter was written at a time when only manually configurable research and laboratory Raman systems were available.

Today, handheld dedicated Raman devices like the Thermo Scientific™ TruScan™ RM analyzer have emerged to address specific challenges of incoming identity testing in the pharmaceutical industry. Since these devices have no user-configurable hardware, a number of <1120> components relating to hardware function settings and tuning do not apply. This document calls out the components of USP <1120> that pertain to material identity testing, our interpretation of the statements (where necessary), and the TruScan RM analyzer's respective capabilities. Text in italics is always a direct quote from USP <1120>.

Requirements Assessment

Precautions with Laser Light:
The danger of using high-powered lasers must be recognized, especially when their wavelengths are in the NIR and, therefore, not visible to the eye. Fiberoptic probes should be used with caution and with reference to appropriate government regulations regarding lasers and laser classes.

- TruScan RM analyzer capability: The analyzer's laser is class IIIb under the FDA CDRH classification system. The beam's focal point is directly in front of the nose cone and then diverges rapidly; it is eye-safe outside of 14 inches. Country-specific regulations with which the analyzer's laser complies can be found in appendices of the TruScan RM analyzer User Manual.

Wavelength (X-axis) Calibration:
Most dispersive instruments utilize atomic emission lamps for primary wavelength-axis calibration…. For dispersive Raman instruments, a calibration based on multiple atomic emission lines is preferred.… The laser wavelength must… be confirmed to ensure that the Raman shift positions are accurate for.… dispersive Raman instruments. A reference Raman shift standard material such as those outlined in ASTM E1840-96 (2002) or other suitably verified materials can be utilized for this purpose.… The software provided by the vendor might measure the laser wavelength and adjust the laser wavelength appropriately so that this peak is at the proper position … Wavelength tolerances can vary depending on the specific application.

- TruScan RM analyzer capability: The analyzer is calibrated at the factory directly in accordance with ASTM E1840-96 (2002). Cyclohexane, acetonitrile/toluene (50/50) and acetaminophen bands are used to determine the x-axis calibration of the system. This calibration is verified with cyclohexane, acetaminophen (4-acetomidophenol) and polystyrene, along with additional product release testing. All of these materials are recommended in ASTM E1840-96 (2002). The laser is also directly calibrated to zero (0) wavenumbers at this time and continuously monitored thereafter with automated compensation in software.

Intensity (Y-axis) Calibration:
Calibration of the photometric axis can be critical for successful quantification by using certain analytical methods (chemometrics) and method transfer between instruments.

- TruScan RM analyzer capability: The analyzer is capable of performing quantitative analysis. To enable method transfer between instruments, the analyzer is calibrated at the factory using an externally-placed white light source in full accordance with 'method A' in <1120>.

Furthermore, the TruScan RM analyzer is not a laboratory instrument. It includes a self test function that employs an external polystyrene, acetaminophen, benzonitrile, cyclohexane, or toluene standard sample (choice defined by the administrator in the system settings) to evaluate system suitability at the standard point of sampling. Performance qualification (PQ) regimes may, at the customer's discretion, use additional samples or using the "Instrument Certification" function which employs polystyrene, acetaminophen and cyclohexane standard samples to qualify the system.

External Calibration:
Detailed functional validation employing external reference standards is recommended to demonstrate instrumental suitability for laboratory instruments, even for instruments that possess an internal calibration approach.

- TruScan RM analyzer capability: The analyzer has a self test function that employs a polystyrene sample to evaluate system suitability at the standard point of sampling.

Performance Verification:
The suitability of a specific instrument for a given method is ensured [in part] by... performance verification [performed more frequently than the periodic operational requalification]... When the device is used for a specific qualitative or quantitative analysis, regular performance verifications are made... [P] erformance verification... often employ[s] external standards... In performance verification, a quality-of-fit to an initial scan or group of scans... included in the instrumental qualification can be employed... Comparison of spectra taken over time on identical reference standards... forms the basis for evaluating the longterm stability of a Raman measurement system.

- TruScan RM analyzer capability: The analyzer has both Self Test and Instrument Certification functions. The Self Test function employs either a polystyrene, acetaminophen, benzonitrile, cyclohexane, or toluene standard sample (choice defined by the administrator in the system settings) to evaluate system suitability on a continuing basis. The same standard sample can be used repeatedly. If desired, the resultant p-values can be tracked long-term using external means. The Instrument Certification function employs a polystyrene, acetaminophen and cyclohexane standard samples to qualify the system. Standard operating procedures can be used to define the Self Test or Instrument Certification functions at specified intervals.

X and y-axis qualification:
As with any spectrometric device, a Raman instrument needs to be qualified for both wavenumber (x-axis and shift from the excitation source) and photometric (signal axis) precision.

- TruScan RM analyzer capability: See details on calibration procedure above. Furthermore, the Self Test function of the analyzer is holistic, allowing the administrator the choice of using the polystyrene, acetaminophen, benzonitrile, cyclohexane, or toluene standard sample.

Spectrometer noise, LOD, LOQ, and spectral bandwidth:
At this juncture it is important to note that specific parameters such as spectrometer noise, limits of detection (LOD), limits of quantification (LOQ), and acceptable spectral bandwidth for any given application should be included as part of the analytical method development. Specific values for tests such as spectrometer noise and bandwidth will be dependent on the instrument chosen and the purpose required. As a result, specific instrument tests for these parameters are not dictated in this information chapter.

- TruScan RM analyzer capability: The analyzer is designed to perform category IV assays (identity tests) as detailed in USP <1225>. USP <1225> indicates that the only data element required for category IV assay method validation is specificity. As such, LOD and LOQ are not relevant. Additionally, spectral bandwidth and spectrometer noise are not user defined settings on the analyzer, so it is our interpretation that the DQ and method validation will be sufficient to demonstrate sufficiency for the intended use.

Wavelength (x-axis) accuracy:
It is important to ensure the accuracy of the wavelength axis via calibration to maintain the integrity of Raman peak positions. … The tolerance of wavelength precision that is required for a given measurement should be assessed during the method-development stage.

- TruScan RM analyzer capability: The built-in self test function assesses the accuracy of the x-axis calibration. Since this parameter is not adjustable on the analyzer, it is our interpretation that comprehensive method validation is sufficient to demonstrate that the accuracy of the x-axis is sufficient for the intended use.

Photometric Precision:
The tolerance of photometric precision required for a given measurement should be assessed during the method-development stage.

- TruScan RM analyzer capability: The embedded PASS/FAIL decision algorithm critically evaluates each measurement for relative y-axis intensity and overall measurement uncertainty at the pixel level of the CCD detector. Methods are deemed successful only after testing against methods of like materials to confirm complete selectivity within the library. Via this testing protocol, a full system validation ensures sufficient tolerances have been maintained during method development.

Performance qualification:
The objective of performance qualification is to ensure that the instrument is performing within specified limits with respect to wavelength precision, photometric axis precision, and sensitivity…. The performance verification standard should match the format of the samples in the current analysis as closely as possible and use similar spectral acquisition parameters.

- TruScan RM analyzer capability: End-users are free to use any standard(s) they deem fit for performance qualification and the analyzer's spectral acquisition parameters are automatically determined. Photometric precision and sensitivity are not relevant for qualitative identity testing and hence are not applicable for a TruScan RM analyzer PQ. The integrity of the x-axis calibration is part of every analysis performed by the analyzer, including the self test function.

Tests for wavelength/photometric/laser precision
- TruScan RM analyzer capability: The analyzer's use for quantitative analysis is for investigational and research purposes and is not designed for release testing, thus the suggested tests do not apply.

Laser power output:
For instruments with an automatic, internal laser power meter, the accuracy of the values generated from the internal power meter should be compared to a calibrated external laser power meter at an interval of not more than 12 months… If the instrument design prevents the use of an external power meter, then the supplier should produce documentation to ensure the quality of the instrument and provide a recommended procedure for the above analysis to be accomplished.

- TruScan RM analyzer capability: Laboratory research systems often require very specific power settings for quantitative analysis and specialized experiments. Because of the restricted intended use of the analyzer, the laser power intensity is not user adjustable. An internal monitor is used to assure the output power does not fall below a minimum level, which would result in abnormally slow acquisition times. It is our interpretation that the DQ, method validation and periodic PQ and system suitability measurements (which ensure the output laser power is above a minimum level) will be sufficient to demonstrate suitability for the intended use.

Method Validation:
Fluorescence is the primary variable that can affect the suitability of a method. The presence of fluorescent impurities in samples can be quite variable and have little effect on the acceptability of a material. The method must be flexible enough to accommodate different sampling regimes that may be necessary to minimize the effects of these impurities.

- TruScan RM analyzer capability: The analyzer uses digital filters to reduce the contribution of fluorescence on the analysis of materials. The suitability of this approach should be evaluated for each material during method validation, where it is immediately discoverable.

Reference:
1. USP 39-NF 34 General Chapter <1120>

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