

The NanoRam Hand-held Raman Spectrometer: Full Regulatory Compliance for the Inspection of Raw Materials and Chemicals

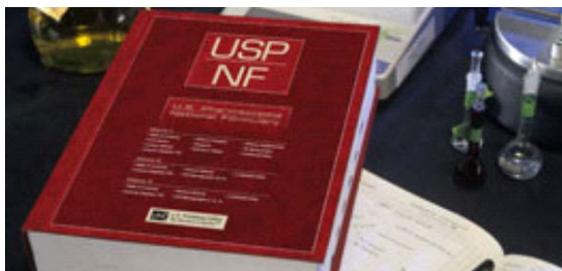
Used in the Pharmaceutical Industry

One of the most critical factors in developing and marketing pharmaceutical drug products and dietary supplements today is ensuring that the analytical methodology used for analysis will produce high quality, valid data, which is used to make sound business and regulatory decisions. Global regulatory agencies like the FDA (Food and Drug Administration), USP (United States Pharmacopoeia) and EP (European Pharmacopoeia), together with Standards organizations such as ASTM (American Standards for Testing of Materials), ANSI (American National Standards Institute) and IEC (International Electrotechnical Commission), have all recognized the importance of this to the drug development process and have separately expanded method validation requirements in recent years. This kind of validation does not only apply to conventional laboratory-based analytical techniques including HPLC, GC, UV/Vis, and IR, but also to in-line, on-line, and portable devices that are used to rapidly check the quality of a product anywhere in the manufacturing process, using on-board spectral libraries and intelligent, decision-making software.



Raman Spectroscopy

In recent years, Raman Spectroscopy is one of the techniques that have gained a reputation in the pharmaceutical industry for the rapid identification of unknown compounds, such as the testing of raw material, verification of active and excipient ingredients, and authentication of the final pharmaceutical product. The reasons behind this surge of interest is that modern Raman instrumentation using state of the art software packages, and on-board spectral libraries, is an ideal technique for molecular fingerprinting purposes. Unlike traditional analytical instrumentation like



HPLC, FTIR and NIR spectroscopy, which requires a high level of operator expertise and more exhaustive sample preparation procedures, Raman equipment can be used in a production environment or for remote field applications because it requires no sample pre-treatment, no direct contact with the sample, and has the unique capability of being able to

test a sample directly through a transparent packing material like glass or plastic. In addition, it requires the user to have virtually no knowledge of analytical chemistry to use the instrument on a routine basis.

Such is the acceptance of Raman spectroscopy in the pharmaceutical industry that it has been referenced by the United States Pharmacopoeia - National Formulary (USP-NF) book of public standards for over fifteen years for the analysis of pharmaceutical materials. More recently, the technique has been incorporated into a new USP chapter (Chapter 1120), which is dedicated to the use of Raman spectroscopy. In addition, the USP has just published a revision of Chapter 197 (Spectroscopic Identification Tests), which allows the use of alternative methodologies such as Raman spectroscopy for the in-line chemical identification of materials, such as active pharmaceutical ingredients (API), excipients, or drug compounds in various stages of the manufacturing process.

NanoRam Handheld Spectrometer



One of the most accomplished of these compact, hand-held Raman spectrometers for the inspection of raw materials and chemicals is the NanoRam® (B&W Tek, Newark, DE, USA). The NanoRam is a state-of-the-art, hand-held Raman spectrometer weighing just 1 Kg (2.2 pounds) for material identification and verification within regulatory-compliant environments. Designed

specifically for existing employees with minimal training, it allows rapid development of standardized and validated methods according to established and accepted procedures within the chemical industry in general and pharmaceutical in particular to facilitate inspection for purity and quality purposes. Once the instrument is loaded with a library of the materials to be identified, verified or validated, the NanoRam can confirm the identity of any material within in seconds, making it the ideal choice for incoming raw materials validation, verification of the final manufactured product, or checking for counterfeit drugs out in the field.

Connectivity

Another key benefit of the NanoRam is the instrument's unique synchronization capabilities within a network, where it can wirelessly communicate in real time with a company's Enterprise Resource Planning (ERP) and/or Quality Management System (QMS) software platform. This allows the users to keep their devices updated with spectral libraries, or to upload validation methods and reporting templates at any time with total security and data integrity. In addition, it has the capability of carrying out method and data interrogation remote from the sampling and testing area via a computer or even a personal tablet device such as an iPad®.

Optical Performance

At the heart of the NanoRam is a 785 nm wavelength laser excitation source with a crossed Czerny-Turner spectrometer and a unique -temperature controlled- CCD detector, providing a very stable signal with low background noise and unmatched data reproducibility. Coupling this proprietary thermoelectric cooling CCD detector from B&W Tek with patented CleanLaze® laser stabilization technology and high speed micro-processor, it provides laboratory-grade Raman performance in a convenient hand-held package. It has the capability of generating a signal with an extremely high signal to noise specification, which is required for the successful testing of materials found in the pharmaceutical industry, and to assure to a maximum level of reproducibility and identify almost all incoming material. This kind of performance delivers a signal of the highest quality, even for complex polymorphic drug compounds, reducing the need for repeated testing of the material, which saves time, decreases production costs and enhances productivity. And for applications that are more complex in nature, or if there is a need for the analyses that are quantitative in nature, intelligent chemometrics software packages and other software development kits (SDKs) are available.

Regulatory Compliance

The instrument comes operational with B&W Tek's proprietary NanoRam OS software, which is compliant with both cGMP and 21CFR part 11 certifications and meets all regulatory requirements for the major global testing agencies. And specifically related to the pharmaceutical industry, the NanoRam is fully compliant with regard to the integrity, safety and traceability of all data generated in the identification and testing of drug compounds and the raw materials as set down by the following standards authorities:

- ✓ United States Pharmacopoeia (USP)
- ✓ European Pharmacopoeia (EP)
- ✓ Japanese Pharmacopoeia (JP)
- ✓ Indian Pharmacopoeia (IP)
- ✓ United States Food and Drug Administration (FDA)



The importance of compliance with FDA guidelines in pharmaceutical manufacturing cannot be over-emphasized. In March 1997, Title 21 of the Federal Regulations, which governs foods and drugs, issued the final Part 11 regulations that provided criteria for acceptance of electronic records, electronic signatures, and handwritten signatures executed electronically as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA programs, are intended to permit the widest possible use of state-of-the-art electronic technology, compatible with FDA's responsibility to protect the public health and to ensure that abuse, falsification, or inadvertent

corruption of electronic data is prevented. As such, 21 CFR Part 11 sets forth the detailed requirements that computerized systems need to fulfill in order to allow electronic signatures and records in lieu of handwritten signatures on paper records. In summary, the regulations apply to:

- Validations for closed and open computerized systems
- Controlled access to the computerized system
- Content integrity
- Use of electronic signatures for authentication of electronic documents
- Audit trails for all records/signatures
- Storage and access to electronic records

B&W Tek's implementation of procedures complying with these requirements include the appropriate administrative controls to ensure that persons who develop, maintain, or use electronic records and signature systems have the education, training, and experience to perform their assigned tasks. In addition, compliance with 21 CFR Part 11 requires designing and embedding appropriate technical controls in the instrumentation to ensure the integrity of system operations and information stored in the system, as well as maintain appropriate audit trails.

The NanoRam has also been designed to be fully compliant with all the major global regulatory, standards, and testing agencies with regard to the safety, reliability and calibrated operation of spectroscopic equipment using laser technology. Some of the leading standards agencies that have specific chapters dealing with the use of Raman instrumentation include:

- ✓ National Institute of Standards and Technology (NIST) – for reference materials
- ✓ American Standards for Testing of Materials (ASTM) – for international standards
- ✓ American National Standards Institute (ANSI) – for safety and the environment
- ✓ International Electrotechnical Commission (IEC) – for safety and the environment

Additionally, B&W Tek offers advice on how to adhere to the following EU directives correctly: the European Union (EU) directives - RoHS (Restriction of Hazardous Substances), Revision 2011/65/EU for the disposal of hazardous materials; and the WEEE (Waste of Electrical and Electronic Equipment Directive), Revision 2002/96/EC for reusing, recycling, or recovering these materials.

B&W Tek also offers both IQ (Installation Qualification) verification by way of documented proof that the equipment has been installed in accordance with relative drawings and specifications under the guidelines of the appropriate safety regulations Also offered is OQ (Operational Qualification) verification which establishes that all process equipment and sub-components are fully capable of operation within the limits and tolerances specified. This kind of support is available to all users of the equipment, together with customized training courses covering the analytical methodology required for specific applications.

Final Thoughts

The NanoRam is a state-of-the-art, handheld Raman spectrometer for the rapid identification of various chemicals used in the pharmaceutical manufacturing process, including the verification of incoming raw materials, quality control of the final drug product and testing of counterfeit drugs in the field. It has been specifically designed for these kinds of applications and for that reason is fully compliant with all the major global regulatory, safety, and commercial testing agencies which are applicable to the pharmaceutical industry. However, for more detailed information about the instrument and in particular the relevant regulatory standards, chapters and directives, please refer to the specific documents cited in the reference section.

Further Reading

- NanoRam data sheet: http://www.bwtek.com/support/distributor/datasheets/Current/280001222-B01_NanoRam.pdf
- Small But Perfectly Formed: World Pharmaceutical Frontiers article - http://www.worldpharmaceuticals.net/marketresources/021/WPF021_bandwtek.html
- The Advantages of a Compact, Thermoelectrically-Cooled Fiber Optic Spectrometer for Raman and Fluorescence Spectroscopy - <http://reg.accelacomm.com/servlet/Frs.FrsGetContent?id=50140727>
- General Compliance statement of NanoRam handheld Raman spectrometer – contact B&W Tek for document
- Support for 21 CFR Part 11 Compliance of NanoRam handheld Raman spectrometer – contact B&W Tek for document