

Metrohm White Paper

Near-infrared spectroscopy in compliance with pharma regulations



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Near-infrared spectroscopy is recognized by common pharmacopoeias as a secondary method for a fast and reliable, non-destructive analysis in pharmaceutical manufacturing. This White Paper explains how Metrohm solutions comply with regulatory requirements.

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Introduction

The pharmaceutical industry is unique with its extensive regulations. Decisions concerning quality assurance are usually made on the basis of regulatory requirements and guidelines. Quality control takes a central role in the pharmaceutical industry. In addition to being robust and reliable, the means of quality control therefore must be maximally efficient. Time-saving secondary methods have therefore come into the focus of both the pharmaceutical industry and regulatory authorities.

Near-infrared spectroscopy (NIRS) is a secondary analytical method that has been explored and used in the pharmaceutical industry since early 1960 [1], e.g., for raw material identification, process control, and quality assurance of final products. This analysis technique is very fast, non-destructive, and requires little to no sample preparation. Meanwhile, it acquires information on both chemical and physical sample properties in each measurement. From the data acquired in a single measurement, multiple parameters can be determined – qualitatively or quantitatively. Because of its short measuring times and the non-destructive nature of its measurements, the full potential of NIRS unfolds, in particular, in process control [2]. NIRS is positioned as «a highly relevant tool for achieving control when built-in quality is preferred over quality by testing» by the U.S. Food and Drug Administration (FDA), the Process Analytical Technologies (PAT) initiative, guidelines by the European Medicines Agency (EMA), and the International Conference on Harmonization in the standards (ICH) Q8(R2), ICH Q9 and ICH Q10 [1].

NIRS applications

NIRS is a versatile analysis method and can be used for a vast number of applications throughout the pharmaceutical manufacturing process. In the following, some example applications will be explored with respect to their benefits for production and their compliance with regulations.

Incoming materials inspection

According to FDA CFR 211.84 and EU GMP 8, all incoming materials have to be tested for verification of the identity and for conformity, thus resulting in a large amount of samples. The Metrohm spectrometer product portfolio offers suitable solutions for a convenient inspection of incoming materials whether they are analyzed directly in the warehouse, in the weighting area or in the QC lab [3, 4].

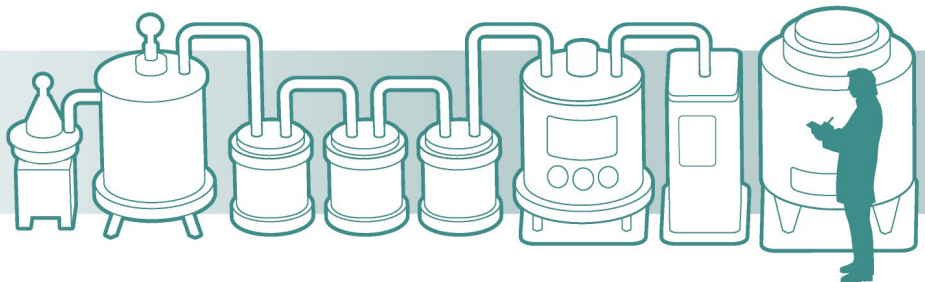
Inline/online process control

Inline/online process control allows less out of specification products manufactured and less rework time to be spent. With Metrohm NIRS inline/online analyzers, real-time monitoring and optimization of, e.g., viable cell density or drying processes can be achieved. Residual solvent and water content in powders and granulates, such as in lyophilized products, can be determined reliably during the production process [3, 5–7].

Incoming raw material



Manufacturing process



Atline, at warehouse

atline, inline, online

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Atline/offline process and product development

Using Metrohm NIRS Analyzers, atline and offline processes like intermediate and product assays or blending and granulation can be monitored [6, 7, 9]. Blend homogeneity and, thanks to real-time process monitoring, the optimum granulation time can be assessed. Furthermore, the content uniformity in solid dosage forms (tablets and capsules) can be determined, as well as tablet characteristics like hardness, stability, etc. [10-14].

Quality assurance of finished products

NIRS allows quality assurance of finished products, such as content determination in creams, gels, tablets, capsules, etc. In addition, the full transmission spectrometer Metrohm NIRS XDS MasterLab guarantees reliable and highly accurate results when investigating active pharmaceutical ingredients and excipients in tablets (even in blisters) to assure that they fulfil the requirements toward purity as well as chemical and physical properties [10-14].

Validation of NIRS

For NIR spectroscopy to be used, software, instrument, and method have to be validated [1]. Regulatory authorities like FDA, EMA, and the U.S. Pharmacopoeia (USP) have published guidelines on how to develop, validate, submit, and maintain NIRS analytical procedures to ensure full validation and fulfillment of the requirements. While the validation process takes some time and effort, this pays off quickly. The short analysis times and the real-time process monitoring that NIRS offers result in a high return on investment.

Software validation

A software that complies with applicable regulations, such as FDA 21 CFR Part 11 (Electronic records; electronic signatures) and/or EU Annex 11 (Computerized Systems), is qualified to be used in any GMP/GLP environment.

Metrohm NIRS applications

Metrohm offers extensive application support for the pharmaceutical industry, all over the world.

Find the applications you need here: [Application Finder](#).

Metrohm Vis-NIR spectroscopy software

Metrohm Vis-NIR spectroscopy software Vision Air fulfills all technical requirements mentioned in the FDA 21 CFR Part 11 and the EU Annex.

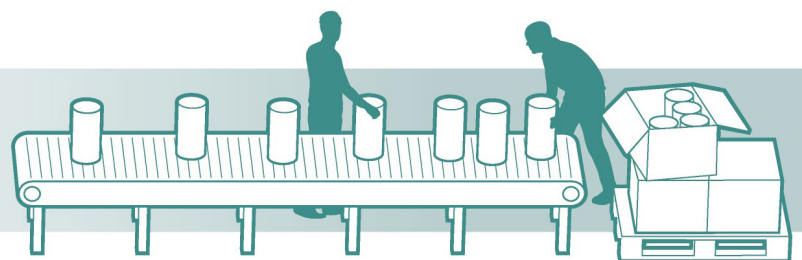
Further details on how the different requirements are solved in Vision Air are presented in the Metrohm Whitepaper «Regulatory compliance in pharma: Software requirements and solutions».

Quality control laboratory

 **Metrohm**
NIRSystems

Packaging

 **Metrohm**
NIRSystems



offline, at lab

offline, atline

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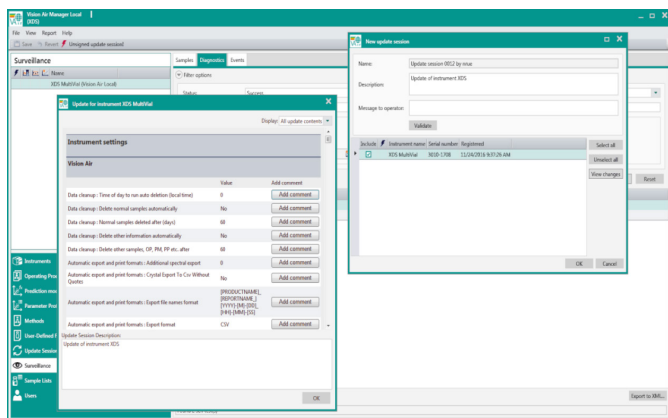


Figure 1. Report view in Vision Air.

Instrument qualification

The validation process of instruments consists of three phases according to USP<1058> and GMP/GLP:

Installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

IQ: According to USP<1119>: «The IQ requirements help ensure that the hardware and software are installed according to vendor and safety specifications at the desired location.» [15].

OQ: According to USP<1119>: «The instrument's performance is controlled with respect to external certified standards to verify that the system operates within target specifications. The purpose of OQ is to ensure that an instrument is suitable for its intended application. (...) Similar to any spectrophotometric device, NIR instruments need to be qualified for both wavelength and photometric scale. Maximum and reduced light-flux noise tests are also included.» [15].

PQ: According to USP<1119>: "A quality to fit to an initial scan or group of scans included in the operational qualification is employed. In such an analysis, it is assumed that reference standard spectra collected on a new or a newly repaired, properly operating instrument represent the best ones available. Comparisons of spectra taken over time on the identical reference standards from the basis for evaluating the long-term stability of an NIR measurement system. The objective is to ensure that no wavelength calibration shift of change in sensitivity occurs during ongoing analysis." [15]. Usually, PQ is performed by the laboratory personnel [1].

Metrohm qualification

Metrohm's Analytical Instrument Qualification for NIRS instruments meets all requirements mandated by many governing bodies (USP<1058>, USP<1119>, GAMP, 21 CFR Part 11, PIC/S, etc.). The high-quality support that Metrohm is famous for includes professional installation and startup of new instruments in compliance with Installation Qualification (IQ) and guarantees that Metrohm NIRS instruments meet Operational Qualification (OQ) requirements, including complete documentation. Metrohm provides instrument performance certification and work-related training of users with subsequent certification.



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Method validation

After the validating the software and hardware, the methods are developed – and validated as well. The main reason for method validation is to guarantee and prove the suitability of an analytical procedure [2]. Each step of the method development, method validation, and method transfer has to be documented in a transparent way. According to Ciurczak, «(...) the development laboratory must provide the end user or designated laboratory with the following documentation:

- A written procedure
- A method validation report
- System suitability criteria» [1].

Summary & support

Near-infrared spectroscopy (NIRS) is an established secondary analysis method for offline, atline, online, and inline applications in the pharmaceutical industry. Once NIRS is validated, it is cost- and time-effective and, thanks to its high return on investment, pays for itself quickly.

Metrohm NIRS solutions and software enable pharmaceutical analyses that are compliant with common regulations. Customers who choose to implement a Metrohm NIRS solution benefit from extensive support in method and application development, among others.

Metrohm's method validation

Metrohm's Vis-NIR spectroscopy software Vision Air Complete includes features for method validation. The chemometric software Vision and supported 3rd party tools such as CAMO's Unscrambler and PLS_Toolbox by Eigenvector Research allow to perform the development and the validation of identification, qualification, and quantification methods.



Figure 2. Report of the USP Wavelength Accuracy Test from Vision software (left) and used Metrohm NIRS XDS SmartProbe Analyzer with standard (right).

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References

- [1] E.W. Ciurczak and B. Igne, Pharmaceutical and Medical Applications of Near-Infrared Spectroscopy (CRC Press, Boca Raton, Florida, 2015).
- [2] N. Broad, P. Graham, R. Hailey, A. Hardy, S. Holland, S. Hughes, D. Lee, K. Prebble, N. Salton and P. Warren, Guidelines for the Development and Validation of Near-Infrared Spectroscopic Methods in the Pharmaceutical Industry, Handbook of Vibrational Spectroscopy (John Wiley & Sons, Chichester, 2002)
- [3] Using NIR as an identification technique of raw materials and product materials, Application Bulletin AB-410
- [4] Identification of pharmaceutical raw materials, Application Bulletin AB-410
- [5] Robert Mattes et al., Monitoring viable cell density in bioreactors using near-infrared spectroscopy, BioProcessing Journal, 2010
- [6] Near-infrared spectroscopy for monitoring a single-pot granulator, Application Note AN-NIR-016
- [7] Monitoring the purity of recovered solvents with NIRS, Application Note AN-NIR-021
- [8] Analysis of residual moisture in a lyophilized pharmaceutical product by near-infrared spectroscopy (NIRS), Application Bulletin AB-358
- [9] Following the progress of pharmaceutical mixing studies using near-infrared spectroscopy, Application Note AN-NIR-014
- [10] Nondestructive, single tablet analysis using the NIRS XDS RapidContent Analyzer, Application Note AN-NIR-002
- [11] Nondestructive, single tablet analysis using the NIRS RapidContent Analyzer, Application Note AN-NIR-002
- [12] NIRS "predictive model" for the release of pharmaceutical active ingredients from solid dosage forms, Application Note AN-NIR-017
- [13] Near-infrared (NIR) assay and content uniformity of tablets, Application Note AN-NIR-018
- [14] Determination of active ingredients in solid (pharmaceutical) dosage forms utilizing solid-state standard additions, Application Note AN-NIR-001
- [15] Near-Infrared Spectroscopy, <1119>, USP 39 (2016)