FDA 21 CFR Part 11 Requirements for NIR Spectroscopy

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The prosperity of a society can be evaluated based on many criteria, and the focus is certainly different for each individual. However, the factor everybody will unhesitatingly agree with is health. When sick, we can nowadays fall back on high-performing, high-quality drugs. To ensure this good quality, powerful analytical instruments such as spectrometers are typically used to monitor their production. Standardization organizations put forward requirements for the use of these instruments. These requirements, with a focus on those concerning software, are presented in this white paper.

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Metrohm

General overview CFR Part 11

Records and signatures in regulated environments can be either created on paper or electronically. In the past, the use of paper has been favored over electronic records and signatures.
Advantages of electronic records compared to paper-based records are cost savings due to a reduced need for personnel to manage and maintain the files, an increase in data security, and as well improved accuracy.

For electronic records and signatures to be eligible for the regulated environment, electronic signatures have to be trustworthy and reliable to an extent that is equivalent to paper records and handwritten signatures. Therefore, defined features have to be implemented within the used software application for the creation of these electronic records. These are described by the Title CFR Part 11 of the Code of Federal Regulation formulated by the US Food and Drug Administration (FDA):

CFR - Code of Federal Regulations Title 21

In the following sections, features of the Metrohm spectroscopy software Vision Air Pharma are used to present software requirements set by the FDA for regulated industries.

The topics discussed in the CFR Part 11 can be catagorized into two groups: firstly, electronic signatures and user management, and secondly, records and audit trails.

This white paper is catagorized in the same manner with a first description how electronic signatures and the user management are organized in Vision Air Pharma.

Electronic signature & user management

11.50 Signature manifestations

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
(1) The printed name of the signer;
(2) The date and time when the signature was executed; and
(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included in human readable form of the electronic record (such as electronic display or printout).

Sample Report

Metrohm NIRSystems

Sample Information	
Operating Procedure:	Data collection
Analysis time:	11:32:19
Analysis date:	21-01-2017
Sample handling:	Small cup (stationary)
Sample number:	Sample-0002
Signature:	476B-2C01
User	Jakob Schultz (jsch)

Parameter	Wa ter Content %							
Data collectio n	5.6 %							

Signatures

Level	Ti mestam p	Name	Reason	Comment
1	2017-01-21 10:32:31	Jakob Schultz (jsch)	Measured according to SOP	
2	2017-01-21 10:31:58	Frank Walter (frwl)	Approved	

2017-01-21 15:13:42 Page 1 of 1

Figure 1. Display of a typical Sample Report created with Vision Air Pharma.

Vision Air offers customized as well as predefined reports. These include sections linked to the digital signature which indicate the ID and the name of the signer, a time-stamp and the meaning of the signature (see figure 1). Signature meanings are managed within the organization.

11.70 Signature/record linking.
Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

11.100 (a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

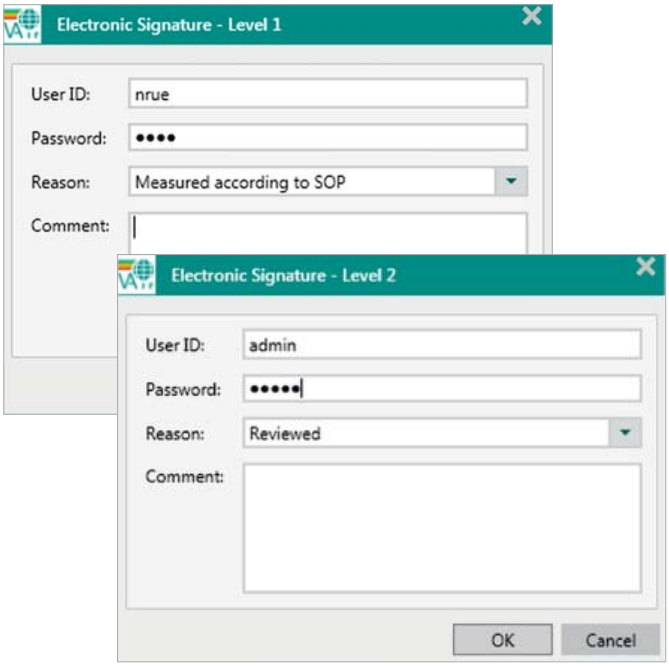

Figure 2. Within each step of the signing process in Vision Air Pharma a User ID, a password and a reason have to be entered. User IDs have to be different for the two signing levels.

In Vision Air Pharma, electronic signatures are linked to unique user IDs and passwords and are therefore specific to one person. Because they are stored in the database, electronic signatures cannot be excised, copied, or transferred. Users with appropriate rights can revoke electronic signatures; however revocation needs to be signed as well and is documented together with the time, the user ID, the name, and the reason for revocation.

Signature	Timestamp	User ID	Name	Reason
Withdrawn	1/17/2017 4:25:27 PM	admin	Herbert Schwarz	Error in configuration
Level 2	1/17/2017 4:25:13 PM	nrue	Nicolas Ruehl	Validated
Level 1	1/17/2017 4:25:06 PM	admin	Herbert Schwarz	Configuration reviewed

Figure 3. Vision Air Pharma audit trail with respect to electronic signatures.

11.200 (a) Electronic signatures that are not based on biometrics shall:
(1) Employ at least two distinct identification components such as an identification code and password.
(2) Be used only by their genuine owners; and
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals

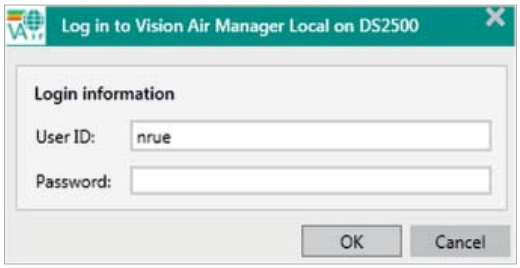

Figure 4. Mandatory Log in procedure during startup of Vision Air Pharma.

Vision Air demands a user ID and password for login into the software. This is a first check of the user who uses electronic signatures. In addition, a login and password combination has to be entered for every signature.
Each signing process can consist of up to two levels, which need to be performed by different individuals.

11.10 (d) Limiting system access to authorized individuals

11.10 (g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

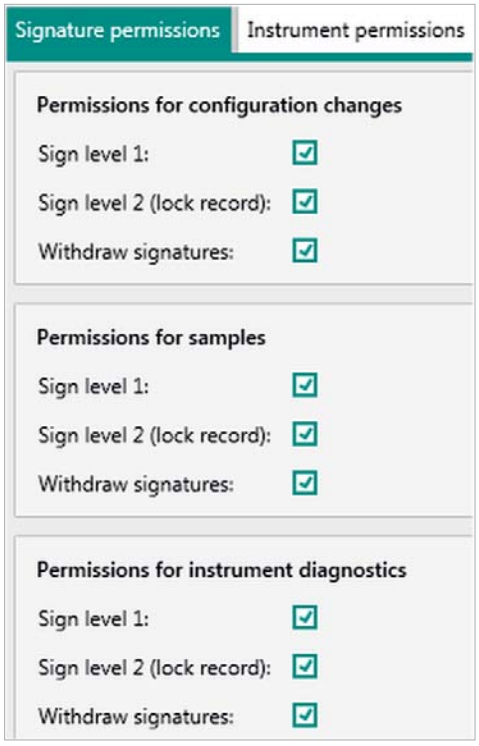

Figure 5. Display of user rights in Vision Air Pharma regarding electronic signatures for "Administrators". Rights can be adjusted for the individual user group.

Each user has a unique ID and password in Vision Air. Three user types can be defined with different access authorities. In addition, password complexicity, length, and the valid time period are set.

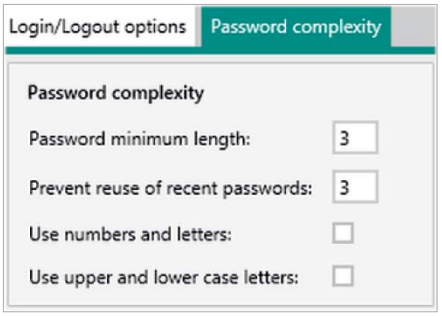

Figure 6. Setting options in Vision Air Pharma regarding password complexity. The minimum settings for the password length and the reuse of recent passwords is three.

11.300 Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled or revised (e.g. to cover such events as password aging).

(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and / or identification codes,and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

Every User ID in Vision Air is unique and cannot be deleted once created but only be disabled. After a defineable number of unsuccessful login attempts, a user is locked. Such critical events are logged in the audit trail. Additionally, selected users can be notified by an automatically generated email.

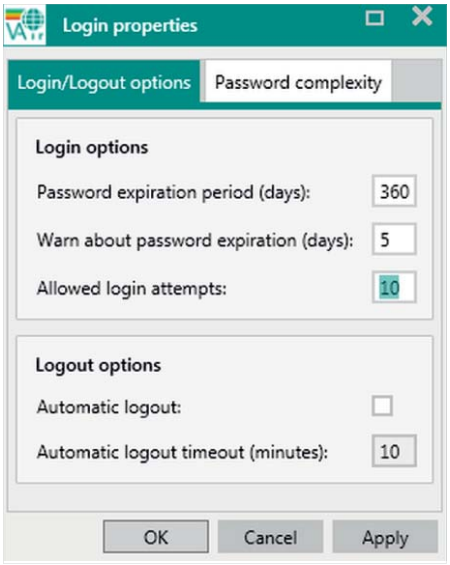

Figure 7. Display of user Login/logout options. Automatic logouts will not cancel measurements.

Electronic records and audit trails

111.10 (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

In Vision Air, an extensive configuration change viewer displays a clear overview of all changes affecting the instrument and the measurement process. User name, date, time, and the reasons for the changes are included in the reports. In addition, the implemented surveillance function gives a complete overview over all measurements, user events, and performed instrument diagnostics.

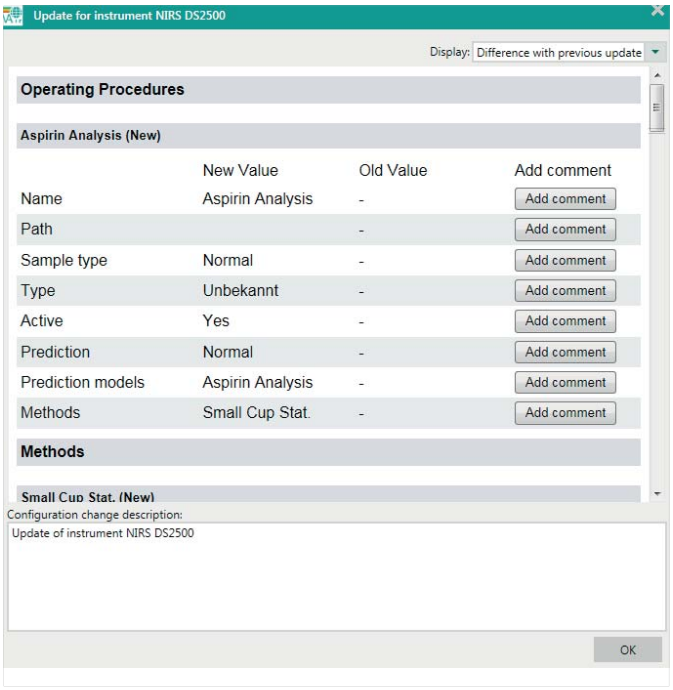

Figure 8. Display of the configuration change viewer after a new operating procedure has been created. Configuration changes need to be signed before being active.

11.10 (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

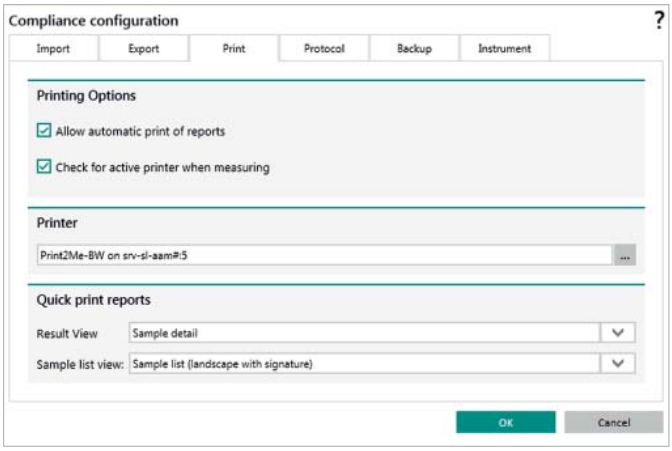

Figure 9. Setting options in Vision Air Pharma for automatic export of files and reports e.g. to a LIMS system. Settings can also be set for an automatically print out of reports.

All instrument settings, users, electronic records, measurements are saved in a SQL database. Electronic records can be created manually or automatically after each measurement. Records can be automaticallly printed and stored. The export folder can be selected to be on a local device or on a network drive. Different file formats for electronic
Every User ID is unique and records are available e.g. PDF, DOC.

11.10 (c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

Vision Air, as a dabased software solution, saves all records (operating procedures, sample data, audit trails, user configurations) in an SQL database. An automatic backup procedure can be set up in Vision Air.

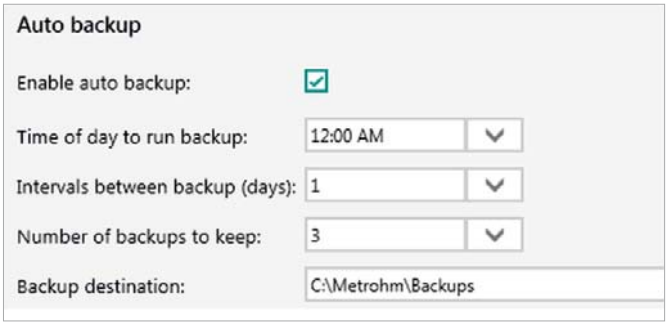

Figure 10. Auto backup settings. Backups are performed even if Vision Air Pharma is closed or users are logged off from the operating system.

11.10 (f) Use of operational checks to enforce permitted sequence of steps and events, as appropriate.

By using operating procedures, Vision Air ensures that all steps of an analysis are performed in the correct order. Guidance is given by mandatory sample registration fields, which have to be filled out by the user during measurement.
Users are also guided in the process of changing configurations. Configuration changes can only be applied after performing a two-level signing process, which has to be done by two persons.

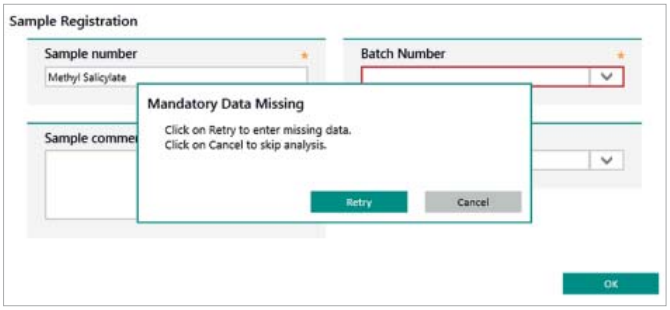

Figure 11. Display of user guidance in Vision Air Pharma. Information in mandatory fields (highlighted in red) need to be entered to complete the sample registration.

Summary
Fulfilling the requirements for the regulated environment is a time-consuming and complex process, which requires the implementation of technical, administrative, and procedural controls. Vision Air offers all technical requirements demanded by the 21 CFR Part 11 to support customers working in regulated environments in achieving and maintaining compliance more quickly and easily.

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