PHARMACEUTICAL REGULATIONS | WHITE PAPER

21 CFR Part 11
Implementation
speedwave XPERT

Compliance for FDA 21 CFR Part 11 and EU Annex 11 supported by the speedwave XPERT

To sell products in the Unites States the compliance with the regulation 21 CFR Part 11 is mandatory for pharmaceutical companies and gets more and more important in the food, feed and cosmetics industry. To achieve compliance with 21 CFR Part 11 systems need to be qualified within the users environment. Therefore, it is reasonable to partner with the instrument manufacturer or vendor to accomplish compliance. The user should specify the requirements to fit the instrument or system into their organization. The manufacturer knows how to setup and qualify the instrument and has to create the technical conditions and functionality of the software.

Berghof Products + Instruments GmbH as instrument manufacturer offers a dedicated 21 CFR Part 11 software upgrade package for the speedwave XPERT and a qualification package including IQ and OQ documentation.

21 CFR Part 11 is a complex regulation, requiring access control, tracking of actions and traceability to be implemented into the instrument software to ensure compliance. It defines the measures to be taken to protect the integrity, and reliability of the electronic records.

This document helps to determine how the speedwave XPERT meets the technical requirements for CFR 21 Part 11 compliance.

Table of content

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

1 Conformity upgrades for the speedwave XPERT

The speedwave XPERT software upgrade features the technical controls making it 21 CFR Part 11 compliance ready and the IQ/OQ qualification package supports the needs of GMP/GLP regulated labs.

These are the available items:

Compliance upgrade	
Item Num-	**Description**
10000132	**Compliance software** the 21 CFR part 11 compliant software package includes user management, password protection, audit trail, documentation, export- and print functionality.
10000231	**IQ/OQ qualification set** for initial instrument qualification of the speedwave XPERT the set includes: IQ and OQ documentation, master copies, IQ sticker and 2 OQ badges
10000232	**Repeating OQ** for renewal of the instrument qualification of the speedwave XPERT contains: OQ documentation and 2 OQ badges
5306360	**Printer** PCL3 ink-jet printer with ethernet cable, Input voltage: 100-240V; 50/60 Hz

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

2 Requirements of the FDA 21 CFR Part 11

21 CFR part 11 defines criteria for acceptance by the FDA and defines the criteria which electronic records and electronic signatures are considered trustworthy, reliable, and equivalent to paper records and hand-written signatures. It requires FDA regulated industries to implement controls, audit trails, validations, electronic signatures, and documentation of software systems involved in processing electronic data.

Where 21 CFR part 11 applies to the companies doing business with the USA, the European Commission has created the Annex 11 for computerized systems to Volume 4 of GMP for the European market. Similar to the FDA regulation, Annex 11 applies to all forms of computerized systems used where GMP regulations apply. Annex 11 applies when computerized systems replace manual operations to avoid process related risks, decrease in product quality, process control or quality assurance.

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

3 Technical implementation in the speedwave XPERT compliance software

The optionally available compliance software package for the speedwave XPERT covers the needs for user management, password protection, audit trail and documentation as well as export and print functions.

3.1 User management

The user management restricts the access to the instrument software to authorized personnel only. There are three different access levels to protect the speedwave XPERT from unauthorized manipulation. The authorization levels are “user”, “admin” and “sys admin” with defined rights. There is an additional authorization level for service technicians only, which allows to create and change factory methods and to reset the user database to factory defaults.

Authorization	None	User	Admin	System Admin
Select and start method		●	●	●
Create, edit and delete method			●	●
Change and create method in favorites			●	●
Change instrument settings (setup)			●	●
Change name of data file, reset indices			●	●
Select name of data file		●	●	●
Create, delete, lock user			●	●
Delete Audit-Trail data				●
Export, print data			●	●
Delete digestion reports			●	●
Save digestion files				●
Change date				●
Change time			●	●
Activate WebVisu as option 21 CFR Part 11				●

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

Open lid, turn turntable	●	●	●	●
Activate option 21 CFR Part 11			●	●

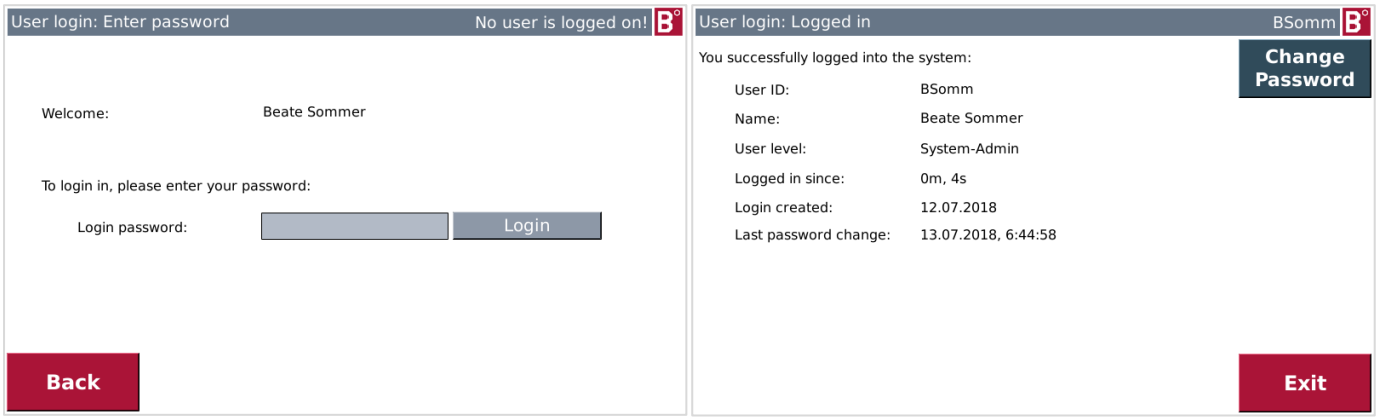
Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

The ID status can be “active”, “inactive”, “new”, “initialization” and “locked”.

- Status “**initialization**”:
  The user must change the initial password to activate the account.
- Status “**active**”:
  An active user can login with ID and password. After verification of the user, one is signed in with the defined rights. An inactive account can be reactivated by an admin and a sys admin. An active user can logout during a running digestion at any time.
- Status “**inactive**”:
  After five unauthorized login trials the ID is deactivated. When an account is inactive it is impossible to login, even with a correct password.
- Status “**locked**”:
  An admin and sys admin is able to lock an account. A sys admin and service account cannot be locked.

3.2 Password protection

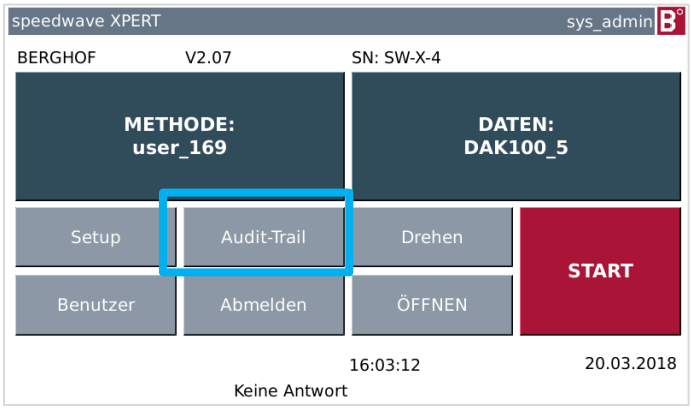
To login an user specific ID and password is required. Each ID contains the given name and the family name of the user. The ID is specific as it is linked to the creation date. The admin can create new users with an initial password, which must be changed by the user at the first login. The admin can activate and deactivate accounts. The user is automatically deactivated after 5 false login trials. All entries and false entries are notified in the audit trail. An admin can reactivate the account. The password expires after 60 days and a new password must be set. The new password must be different from the previous password. The storage of user data is protected from manipulation and read-out.

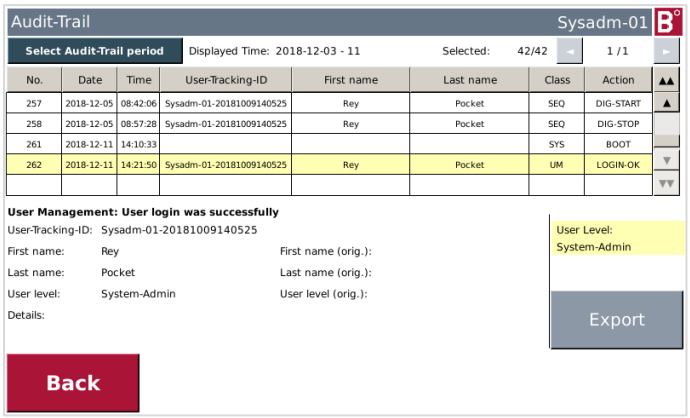


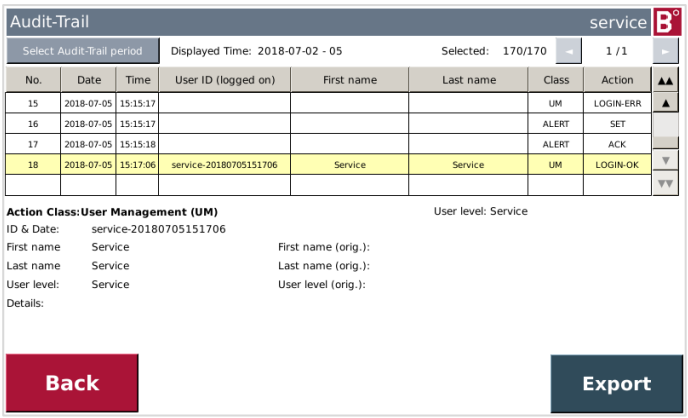
Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

3.3 Audit-Trail

The audit trail tracks all activities, entries and changes performed at the controller.







When the audit trail is retrieved always the last entry is displayed. The table can show up to 500 entries. If there are more than 500 entries in one file, the entries are divided into blocks of 500 each. 

Selected entries are marked in yellow.

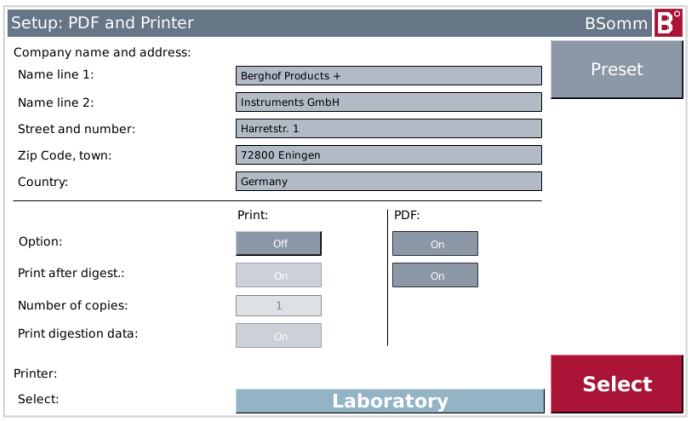
The audit trail provides:

- Data security
- Records of all actions and messages with date and time stamp
- Record of the user ID with appropriate action
- It is continuously written
- Existing entries cannot be over written
- Exportable protected pdf to USB

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

3.4 Export

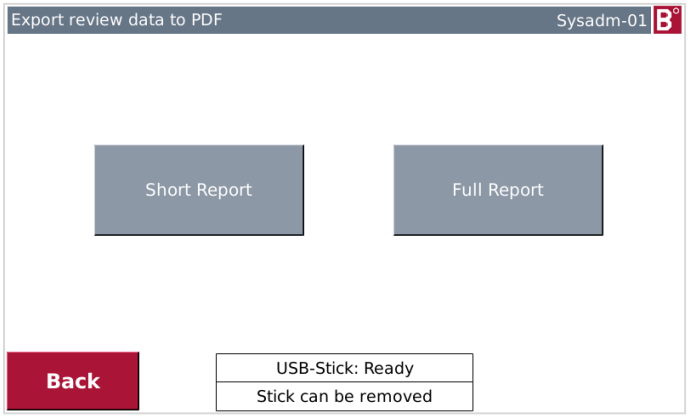
To export data an USB key must be plugged in and the company information must be entered in the setup menu.



The following data can be exported:

- Audit-Trail
- Methods
- User lists
- Digestion reports

The digestion reports can be exported as short and long report. The short report contains basic information and the long report additionally contains also the data table of the whole process.



The export is stored on the USB key as protected pdf and as txt file. The protected pdf is tamper-proof for storage, whereas the txt file is created for visualization in the datarecord viewer.

3.5 Electronical records

pdf file:

- Files are not back readable
- Human readable
- Printable by Acrobat Reader
- encrypted

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

4 21 CFR Part 11 requirements vs. technical implementation of the speedwave XPERT

§11.10 Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine.

Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system

The speedwave XPERT is a closed system. The following table summarizes the requirements of 21 CFR Part 11 for electronic records compared to the technical implementation into the speedwave XPERT:

FDA 21 CFR Part 11 **Subpart B – Electronic Records**				
§	**Term**	**Berghof**	**User**	**Solution**
Controls for closed systems				
§11.10 (a)	Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.	Performance tests and validations are done before the release of a new product in accordance with the internal quality regulations and ISO 9001. - Quality management in place (change management, development process) - ISO certification - Qualification package available	- Assure correct installation and functionality of the instrument - Perform instrument qualification on a regular basis - Instrument is working as expected and functioning - Preventive maintenance is performed - PQ tests	DIN EN ISO 9001 IQ/OQ package Repeating OQ The IQ/OQ documentation is available and ensures correct installation (IQ) and functionality (OQ) as specified by Berghof Templates and guidelines for preventive maintenance

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

(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.	Technical conditions of the instrument to generate audit trail and export and print functionality Provide file exports and generate printable reports Export function for methods, digestions, user lists and audit trail in a unchangeable file formate	Export of reports on a regular basis	All data is stored on the controller of the speedwave XPERT and can be printed and exported as pdf and txt files. Audit trail is automatically generated Data export function contains user and time stamp.

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

FDA 21 CFR Part 11 Subpart B – Electronic Records				
§	**Term**	**Berghof** **responsibility**	**User** **- responsibility**	**Solution** **speedwave XPERT**
(c) (d)	Protection of records to enable their accurate and ready retrieval throughout the records retention period. Limiting system access to authorized individuals.	Access control to instrument functionality and information. Users can be created by an admin within the defined administration levels. The admin defines an initial password, which must be changed by the user, at the next login. User management: - Individual user ID´s - User levels Password protection: - Password expiration - Password security level - User locking after 5 false entries Tracking in audit trail	- Backup of data on a regular basis - Archiving of the exported data on an appropriate medium - Install corresponding reading tool on the relevant PC	User management with access control by user administration (user ID / password) Password protection Password security/complexity rules User identification (ID, first name, last name) Password expiration (60 days) Locking after 5 false entries – activation by admin required Users are able to change the password at any time
(e)	Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be	Audit trail is continuously written and exportable as pdf It contains: - One entry per action - Date and time stamp - Numbering of entries - Serial number - User	Export of reports on a regular basis to a suitable medium	Audit trail entry per activity with time and ID stamp Audit trail entries are not accessible for alteration. The audit trail can be exported as pdf for storage and as csv for easy sorting and filtering

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

	available for agency review and copying.			
(f)	Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.	- Preinstalled factory methods - Error messages - Warning messages	Instructions must be entered in an SOP	Predefined steps in applications and methods Error and warning messages
(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.	- Access control - User management - Audit trail entries	Definition and control of authorized users	Software access control (user ID / password) according to the rights of the account

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

FDA 21 CFR Part 11 Subpart B – Electronic Records				
	Term	**Berghof responsibility**	**User responsibility**	**Solution speedwave XPERT**
(h)	Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.	Hardware is identified via serial number, to ensure that only valid configurations are in use.		Serial number and codings to control allowed device combinations. Listed in the audit trail in the startup information.
(i)	Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.	Berghof assists by individual trainings for customer, distributor and service engineers	Define responsibilities and implement them in the defined level as user, admin or sys admin - Internal trainings to qualify users. - Read the operation manual - Regular instrument qualification (OQ) - Preventive instrument maintenance	
(k)	Use of appropriate controls over systems documentation including: (1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance. (2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.	- Berghof processes requesting hardware and software manuals, updated per release, delivered with product - Change history in all documents - The Berghof quality management assures that hardware and software is tested and revised bevor the release.	- Storage of the documentation - Provide each user access to operation manual - Change and configuration management	- Change history listed in the documents - Operation manuals are delivered with the instrument. - The documentation contains change history, versioning. - IQ/OQ documentation for qualification
Signatur manifestations				

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

§11.50 (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.		Definition of user level as specified	Time stamped audit trail´s identify the corresponding user, containing date, time, name and meaning
(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 as part of any human readable form of the electronic record (such as electronic display or printout).	Export and printout of reports		These information are also contained on report views and printouts

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

FDA 21 CFR Part 11 Subpart B – Electronic Records				
§	**Term**	**Berghof responsibility**	**User responsibility**	**Solution speedwave XPERT**
Signature / record linking				
§11.70	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.	Records cannot be changed. Entry in the audit trail of each activity includes user ID with details of the user		All user activities are tracked in the audit trail (access control)

FDA 21 CFR Part 11 Subpart C - Electronic Signatures				
Reference	**Term**	**Berghof responsibility**	**User responsibility**	**Comment**
General requirements §11.100 (a)	Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.	Accounts can be activated, deactivated or deleted by the admin. Identical ID´s, are impossible as the ID is linked to the creation date and time.	- Administration of the users by the admin - Passwords must not be provided to third persons - User names must not be identical to different users - Export and storage of user lists on a regular basis	User accounts are unique and use individual ID, user name and password

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

FDA 21 CFR Part 11 Subpart C - Electronic Signatures				
Reference	**Term**	**Berghof responsibility**	**User responsibility**	**Comment**
Controls for identification codes / passwords §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). (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	Unique combination of user ID, name and password in the software to create an account. Defined validy period of the password. Tracking of logins and failed logins trials in the audit trail. Invisability of the password during entry	User can be deactivated by an admin. Protection of the password from third persons.	- Password expiration after 60 days - User is locked after 5 false entries and must be reactivated by an admin - Failed logins are recorded and listed in the audit trail - Defined password security level - The new password must be different from the old password

5 Typical questions about 21 CFR Part 11 compliance of the speedwave XPERT

FAQ´s	
Question	**Answer**
Is it possible to create individual user accounts?	Yes, user accounts can be created with individual ID and name within the defined user groups

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany

FAQ´s	
Question	**Answer**
Is it possible to logout when a digestion is running?	Yes
Is there an password expiration?	Yes, the password expires after 60 days and must be renewed.
Will the software be locked after repeated unauthorized attempts?	Yes, after 5 false entries oft he ID and password, the user is locked.
How many users can be logged in at the same time?	Only one.
Is there an Audit Trail to capture all changes and actions?	Yes
Can the Audit Trail file be modified?	No
Is there an export function to safe the records?	Yes, methods, result files, user list and Audit Trail can be exported to USB.

Michaela Buffler | Product Manager | Berghof Products + Instruments GmbH | Harretstrasse 1 | 72800 Eningen | Germany