White Paper

INTEGRA

21 CFR part 11: Electronic Records and Electronic Signatures

Compliance of VIALAB, ASSIST PLUS and Electronic Pipettes

1 Introduction

21 CFR part 11 defines the criteria under which the FDA will accept electronic records and electronic signatures as equivalent to paper-based records and handwritten signatures. These criteria affect institutions reporting electronic data to the FDA, including pharmaceutical and medical device manufacturers, biotech companies, biologics developers, CROs and other FDA-regulated industries worldwide.

As per definition 11.3 of electronic records, pipetting programs stored and created on a computer or a pipette are considered electronic records and thus fall under the regulation.

2 Scope of this document

This document compares the technical specifications of the VIALAB software, associated electronic pipettes and ASSIST PLUS (hereafter named “INTEGRA pipetting system”) against the legal requirements of 21 CFR 11 for electronic records and electronic signatures. This enables the customer to evaluate the INTEGRA pipetting system and take preparative steps to integrate it into a regulated laboratory environment.

The information about CFR Part 11 contained in this document is based on the official release dated April 1 2018 (Website FDA/ CFR Part 11).

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3 Definitions and interactions of INTEGRA software and pipettes

Computerized Pipetting System

PC Software: VIALAB
Create pipetting programs, store pipetting programs

Note: A pipetting program contains all liquid handling parameters, such as volumes and speeds, and pipetting positions. These parameters are instructions for the robot to carry out the actual pipetting process.

Transfer of programs

Electronic Pipettes: VIAFLO, VOYAGER
Create pipetting programs, modify pipetting programs, store pipetting programs

No direct program transfer. Only firmware update.

Pipette sends instructions

ASSIST PLUS with INTEGRA pipette = Pipetting Robot
Pipette is connected via Bluetooth or cable and sends the stored pipetting program to ASSIST PLUS

Pipetting programs are created on the PC with VIALAB and then transferred to the pipette in a proprietary file format via Bluetooth or cable. Basic pipetting programs can also be created directly on the pipette. Commands from both types of programs are then transferred to ASSIST PLUS via Bluetooth or cable. ASSIST PLUS cannot modify programs, it only follows their commands.

Subpart A – general provisions

4 Section 11.3: general definitions

ID	Ref.	CFR part 11 general definition	INTEGRA Statement
4.1	11.3. (b) (4)	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.	INTEGRA's combination of electronic pipettes, ASSIST PLUS and VIALAB is a closed system. Electronic pipettes: pipetting programs are written and transferred to the pipette by the user. Programs are created and accessed using the VIALAB software. ASSIST PLUS only receives pipetting commands from INTEGRA electronic pipettes. VIALAB software: only allows communication with electronic pipettes from INTEGRA. Access to VIALAB can be configured by MS Windows access rights.

4.2	11.3. (b) (5)	Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.	No further explanation.
4.3	11.3. (b) (6)	Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.	Pipetting programs stored on a computer and pipettes are considered electronic records.
4.5	11.3. (b) (7)	Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual‘s handwritten signature.	No further explanation.

Subpart B – electronic records

5 Section 11.10: controls for closed systems

ID	Ref.	Question[1]	Compliant	INTEGRA Statement
5.1	11.10 (a)	Is the system validated?	N/A	INTEGRA’s combination of electronic pipettes, ASSIST PLUS and VIALAB is a closed system. Electronic pipettes: pipetting programs are written and transferred to the pipette by the user. Programs are created and accessed using the VIALAB software. ASSIST PLUS only receives pipetting commands from INTEGRA electronic pipettes. VIALAB software: only allows communication with electronic pipettes from INTEGRA. Access to VIALAB can be configured by MS Windows access rights.
5.2	11.10 (a)	Is it possible to discern invalid or altered records?	No	Changes to pipetting programs are not highlighted and cannot be traced. Programs are saved as XML files on the computer. The user must ensure that the files are protected.
5.3	11.10 (b)	Is the system capable of producing accurate and complete copies of electronic records on paper?	Yes	VIALAB offers the option to export and print PDF files. The PDF reports include all critical details of the pipetting program. Pipetting programs can be saved as XML and PDF files on the PC or network drive and can be archived.
5.4	11.10 (b)	Is the system capable of producing accurate and complete copies of records in electronic form for inspection, review and copying by the FDA?	Yes	VIALAB offers the option to export and print PDF files. The PDF reports include all critical details of the pipetting program. Pipetting programs can be saved as XML and PDF files on the PC or network drive and can be archived.

5.5	11.10 (c)	Are the records readily retrievable throughout their retention period?	Yes	Pipetting programs are saved in a common XML file format and can be exported to PDF.
5.6	11.10 (d)	Is system access limited to authorized individuals?	Yes	The VIALAB software itself has no authorization concept. However, user access rights can be controlled via Windows user administration, allowing folder level authorization to edit program files to be granted. The pipettes themselves can be password protected against program changes and overwrites.
5.7	11.10 (e)	Is there a secure, computer generated, time stamped audit tail that records the date and time of operator entries and actions that create, modify, or delete electronic records?	No	An audit trail is not available.
5.8	11.10 (e)	Upon making a change to an electronic record, is previously recorded information still available (i.e. not obscured by the change)?	No	An audit trail is not available. Accomplished by the customer through organizational measures (change control, report check)
5.9	11.10 (e)	Is an electronic record's audit trail retrievable throughout the record's retention period?	No	An audit trail is not available.
5.10	11.10 (e)	Is the audit trail available for review and copying by the FDA?	No	An audit trail is not available.
5.11	11.10 (f)	If the sequence of system steps or events is important, is this enforced by the system (e.g. as would be the case in a control system)?	No	An audit trail is not available. Realizable by the customer through organizational measures (change control, report check)
5.12	11.10 (g)	Does the system ensure that only authorized individuals can use the system, electronically sign records, access the operation, or computer system input or output device, alter a record, or perform other operations?	Yes No (for pipette)	Only authorized users can log on to the computer and access pipetting program files (controlled via Windows folder permissions and active directory management). Anyone who can log on to the computer can use the software.
5.13	11.10 (h)	If it is a requirement of the system that input data or instructions can only come from certain input devices (e.g. terminals) does the system check the validity of the source of any data or instructions received? (Note: This applies where data or instructions can come from more than one device, and therefore the system must verify the integrity of its source, such as a network of weigh scales, or remote, radio controlled terminals).	N/A	Not a requirement. All inputs to VIALAB come from the user. There is no interface to other systems. VIALAB programs transferred to the pipette are in a proprietary file format. The pipette itself cannot receive data from any device other than a computer running VIALAB. However, the pipette can receive the data from any PC running VIALAB.
5.14	11.10 (i)	Is there documented training, including on the job training for system users, developers, IT support staff?	Yes	INTEGRA offers training for users. Training certificates are not issued to date.
5.15	11.10 (j)	Is there a written policy that makes individuals fully accountable and responsible for actions initiated under their electronic signatures?	No	There are no electronic signatures available.
5.16	11.10 (k) (1)	Is the distribution of, access to, and use of systems operation and maintenance documentation controlled?	N/A	Documentation is the responsibility of the user.
5.17	11.10 (k) (2)	Is there a formal change control procedure for system documentation that maintains a time sequenced audit trail of changes?	N/A	Documentation is the responsibility of the user.

6 Section 11.30: controls for open systems

ID	Ref.	Question[1]	Compliant	INTEGRA Statement
6.1	11.30	Is data encrypted?	N/A	It is not an open system.
6.2	11.30	Are digital signatures used?	N/A	It is not an open system.

7 Section 11.50: signature manifestations

ID	Ref.	Question[1]	Compliant	INTEGRA Statement
7.1	11.50 (a) (1-3)	Do signed electronic records contain the following related information? - The printed name of the signer - The date and time of signing - The meaning of the signing (such as approval, review, responsibility)	No	Electronic signatures are not available.
7.2	11.50 (b)	Is the above information (11.50 (a)) shown on displayed and printed copies of the electronic record?	No	Electronic signatures are not available.
8.1	11.70	Are signatures linked to their respective electronic records to ensure that they cannot be cut, copied, or otherwise transferred by ordinary means for the purpose of falsification?	No	Electronic signatures are not available.

Subpart C – electronic signatures

There is no formal release procedure for pipetting programs. A function to verify and release a program by an authorized person before loading it onto the pipette is not available. There is also no user login on VIALAB or on the pipette level and therefore electronic signatures are not available. Anyone who has access to VIALAB and physical access to the pipettes can upload a program, unless the pipette is password protected, which prevents programs from being uploaded.

8 Section 11.100: general requirements

ID	Ref.	Question[1]	Compliant	INTEGRA Statement
9.1	11.100 (a)	Are electronic signatures unique to an individual?	No	Electronic signatures are not available.
9.2	11.100 (a)	Are electronic signatures ever reused by, or reassigned to, anyone else?	No	Electronic signatures are not available.
9.3	11.100 (b)	Is the identity of an individual verified before an electronic signature is allocated?	No	Electronic signatures are not available.
9.4	11.100 (c)	Did persons using electronic signatures (on or after August 20, 1997) certify to the FDA that their electronic signature is the legally binding equivalent to their handwritten signatures?	No	Electronic signatures are not available.

9 Section 11.200: electronic signature components and controls

ID	Ref.	Question[1]	Compliant	INTEGRA Statement
9.1	11.200 (a) (1)	Is the electronic signature employing at least two distinct identification components, such as identification code and password.	No	Electronic signatures are not available.
9.2	11.200 (a) (1) (i)	When several signings are made during a continuous session, is the password executed at each signing? (Note: both components must be executed at the first signing of a session)	No	Electronic signatures are not available.
9.3	11.200 (a) (1) (ii)	If signings are not done in a continuous session, are both components of the electronic signature executed with each signing?	No	Electronic signatures are not available.
10.4	11.200 (b)	Are electronic signatures based upon biometrics designed to ensure that they can only be used by their genuine owner?	No	Electronic signatures are not available.

10 Section 11.300: controls for identification codes/passwords

ID	Ref.	Question[1]	Compliant	INTEGRA Statement
10.1	11.300 (a)	Are controls in place to maintain the uniqueness of each combined identification code and password, such that no individual can have the same combination of identification code and password?	Yes	Accomplished by Windows user login and administered by IT organisation.
10.2	11.300 (b)	Are procedures in place to ensure that the validity of identification codes are periodically checked?	Yes	It is the responsibility of the user to ensure that passwords are changed regularly.
10.3	11.300 (c)	Is there a procedure for electronically disabling an identification code or password if it is potentially compromised or lost?	Yes	Is the responsibility of the user.
10.4	11.300 (d)	Is there a procedure for detecting attempts at unauthorized use and for informing security?	Yes	Is the responsibility of the user.
10.5	11.300 (e)	Is there initial and periodic testing of tokens and cards?	Yes	Is the responsibility of the user.
10.6	11.300 (e)	Does this testing check that there have been no unauthorized alterations?	Yes	Is the responsibility of the user.

[1] Questions from: Good Practice and Compliance for Electronic Records and Signatures Part 2, Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures; A document produced jointly by ISPE and PDA

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