ADVANCED INSTRUMENTS

Application Note

Introducing Continuous Audit Mode (CAM) on Solentim's STUDIUS^{TM} data management platform

Why a Part 11 'mind set' should be a foundation to every cell line development workflow

Scientists and Quality Managers working in the clinical manufacturing of therapeutics will be familiar with the Part 11 regulations. These either regulate, in the case of the US FDA Part 11, or are key guidelines to compliance as in the case of EU Annex 11. In both cases they describe the requirements for computer systems and digital signatures within cGMP regulated pharmaceutical environments.

The intent of both Part 11 pieces is to best manage the security of electronic records, record attribution of work and define the use of electronic signatures. This design methodology is frequently described as a 'closed system' where all interactions with data (production, changing, removal) are audited and protected from external influence.

In this document, both FDA Regulations and EU guidance are described as Part 11 for convenience. Please note there are differences in both enforcement and guidance between the two and this document should not be used for specific implementation or details of these. For details, please refer to:

- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/annex11_01-2011_en.pdf

Within Part 11, the primary questions are:

Is the data secure?

Does the system make sure that only the right people, have the right access to the right information? In practical terms, systems must be able to identify users and limit access and rights to trained and permitted individuals (regulations 11.10(d), (i) and (g) 11.100b). Within a laboratory staffing structure, access and responsibilities should be segregated and managed such that specific users are permitted to perform specific tasks. In practice, this can mean Managers defining what other staff are permitted or not permitted to do.

Is the data secure?

This aspect relates to auditing of the data. A system such as STUDIUS^{TM} provides automated auditing that independently registers all user interactions with the system, enabling external staff to view a complete history of the electronic data files.

Is the person who provided the signature who they claim to be?

Electronic signatures are not mandatory but where they are used, e-signatures record name, date, time and what was signed off and why. Moreover, how do we know the person who provides the signature is the person they claim to be?

Adopting a Part 11 mindset in the research environment

Part 11 regulations and guidelines were developed for the production and distribution of medical products, not medical devices or research tools. Discovery and cell line development are deemed to operate within the research sphere. A decision on the utility or requirement for Part 11 tools within such research environments is ultimately the decision of each company. However, required or not, the principles described here of data security, auditing and authority have universal benefit both for a laboratory developing processes with a view to scaling up towards clinical manufacturing in the future or just for overall peace of mind that comes from a secure and audited environment. On a practical level, knowing that data hasn't been changed, lost or been generated by someone not qualified or authorised, has considerable practical and peace-of-mind benefits for any commercial laboratory – either for their own internal purposes or when communicating externally to clients or regulatory authorities.

It is therefore increasingly common to see commercial laboratories implement good foundations including aspects of cGMP planning and Part 11 data management within a new lab or new process set up, investing for the future now to save time and money later.

Continuous Audit Mode within STUDIUS data management system

STUDIUS is a data management system designed for cell line development processes. The system manages data derived from Solentim instruments at multiple stages in the process – seeding, whole well imaging and selection – filtering data by clonality, growth and corrected titer.

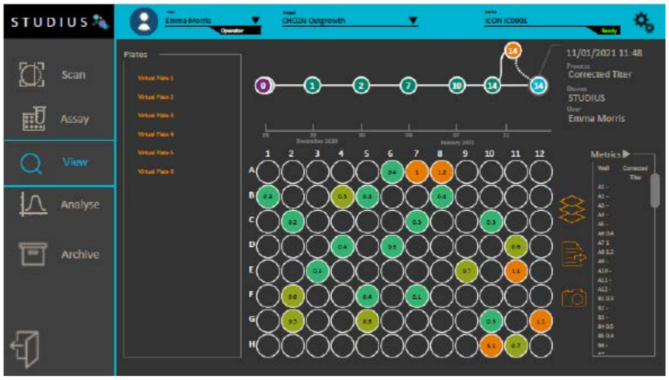
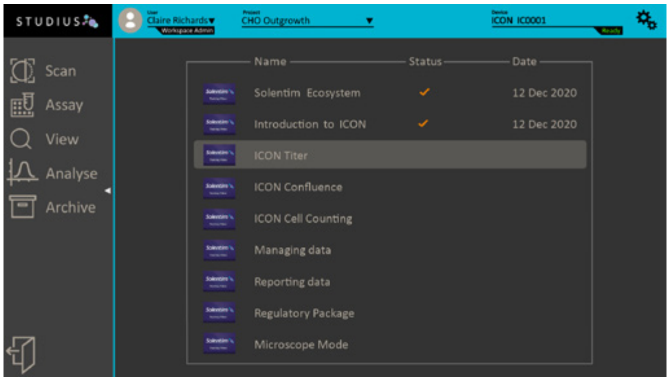


Figure 1. Example of STUDIUS interface showing corrected titer data at day 14 of a cell line development process.

STUDIUS is available with Continuous Audit Mode, a suite of tools designed to accommodate the requirements of Part 11 regulations or guidance.



Name	Status	Date
Solentim Ecosystem	✓	12 Dec 2020
Introduction to ICON	✓	12 Dec 2020
ICON Titer		
ICON Confluence		
ICON Cell Counting		
Managing data		
Reporting data		
Regulatory Package		
Microscope Mode		

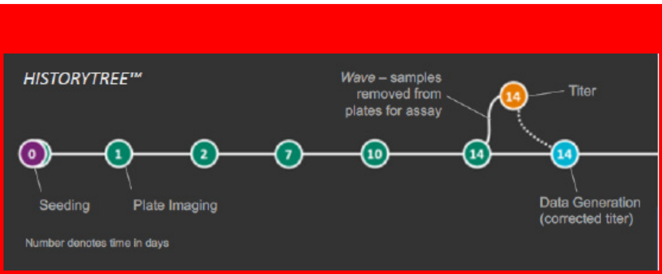
Figure 2. Interface to STUDIUS inbuilt training program which generates a digital signature for the user.

Continuous Audit Mode includes:

- Data stored in a Microsoft SQL Server database. All access security and authentication has been developed using the inbuilt MS SQL Server permission system. This provides accurate and ready retrieval of records following the customer's backup and retention policy.
- Access to the system and database is restricted to users authenticating access with a valid username and password. Access to functionality and data is based on the role assigned to the authenticated user.
- All user actions that create, modify or delete records in
- the software are recorded by the Continuous Audit Module. The audit trail includes the action, who performed it and the date and time it was done. There is no user option to delete audit trail data.
- Inbuilt training and digital certification of users in conjunction with Administrator assigned tasks and responsibilities.

Central to STUDIUS and the implementation of the audit tool is *HISTORYTREE*TM, a graphical representation of data generated at various points of the cell line development process. *HISTORYTREE* acts as a convenient navigation tool within STUDIUS – to scroll left and right through the timeline but is ultimately, a description of the closed data system.

Understanding *HISTORYTREE*


HISTORYTREE™
Wave – samples removed from plates for assay
Titer
0
1
2
7
10
14
14
14
Seeding
Plate Imaging
Data Generation (corrected titer)
Number denotes time in days

Reporting from STUDIUS is ultimately conducted via *HISTORYTREE*. Reporting of data combines information from the audit tool, user information in addition to instrument health and service status to provide a total view of this 'closed' data package.

Technical description of STUDIUS response to CFR Part 11 requirements.

The Code of Federal Regulations Part 11 set forth the criteria under which the FDA considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

When the STUDIUS software is operating in Continuous Auditing Mode (CAM) it can support 21 CFR Part 11 compliance in the following areas:

1.10

- 11.10a) The STUDIUS software has been designed for validation using GAMP-5 processes.

- 11.10b) Authorized users can generate accurate and complete copies of data records.

- 11.10c) All data is stored in a Microsoft SQL Server database. All access security and authentication has been developed using the built in MS SQL Server permission system. This provides accurate and ready retrieval of records following the customers backup and retention policy.

- 11.10d) Access to the system and database is restricted to users authenticating with a valid username and password. Access to functionality and data is based on the role assigned to the authenticated user.

- 11.10e) All user actions that create, modify or delete records in the software are recorded by the Continuous Audit Module. The audit trail includes the action, who performed it and the date and time it was done. There is no user option to delete audit trail data.

- 11.10f) The STUDIUS software has been designed to support structured workflows and enforces the sequencing of steps and events in the workflow as appropriate.

- 11.10g) A combination of username and password are required to access the system, operate the instrument, and electronically sign records.

- 11.10h) STUDIUS is interactive software that enables the user to view images and other generated data. The Continuous Auditing Mode records and displays all instructions that were used to generate the data.

- 11.10i) The STUDIUS software includes comprehensive user guides and videos to assist users in their education and training to use the instrument.

11.50

- The Continuous Audit Module records the performed action, the user who performed it, and the date and time it was done, and the meaning associated with the action. This full information set is displayed wherever signature information is shown.

11.200

- The first time a user signs a record after logging into STUDIUS, they are required them to enter both the parts of their signature (i.e., username and password). Subsequent signings during that same session only require the password to be re-entered. Each time a user logs out and logs back in (or gets timed out by the system), the process restarts, and the first record signed after logging in must require both parts of the signature.

11.300

- STUDIUS requires usernames (identification codes) to be unique across the system. Failed login attempts are recorded and the account locked down after multiple failed attempts. An administrator user is able to disable accounts and reset passwords and identification code.

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For more information on STUDIUS and Continuous Audit Mode, please visit www.aicompanies.com