Technical Information

QIAxcel® Advanced System and 21 CFR Part 11 Regulations

The QIAxcel Advanced system performs fully automated separation of DNA and RNA fragments according to their molecular weight and can process up to 96 samples without user intervention. The QIAxcel Advanced system consists of the QIAxcel Advanced instrument, a computer, a QIAxcel Kit (containing a QIAxcel gel cartridge and reagents), and the QIAxcel ScreenGel Software. All components have been optimized to work together across a wide variety of applications.

Note: The QIAxcel Advanced is intended for molecular biology applications. This product is not intended for the diagnosis, prevention, or treatment of a disease. If QIAxcel Advanced is used with products other than QIAGEN kits, it is the user's responsibility to validate the performance of the product combination for any particular application. The QIAxcel Advanced is intended for use by professional users trained in molecular biological techniques and the operation of the QIAxcel Advanced system.

An increasing number of laboratories are using electronic records (ER) and electronic signatures (ES) for exchanging and storing data. Electronic documentation offers many benefits, including increased efficiency and productivity when storing data and easier information sharing and data mining. If a company or laboratory intends to use an electronic format instead of paper for records that are required under FDA regulations and requirements, the company or laboratory must comply with the regulations issued by the FDA: *Final Rule 21 CFR Part 11 Electronic Records.* ▷

Figure 1. The QIAxcel Advanced System.

QIAGEN

The QIAxcel Advanced is a closed system, where access is controlled by users who are responsible for the content of the electronic records on that system. The software forms part of the ER system by which electronic records are created, modified, stored, and secured against further modification. The QIAxcel Advanced does not provide electronic signature functionality.

The QIAxcel Advanced files shown in Table 1 are electronic records that are affected by 21 CFR Part 11. Compliance of files generated by other software, such as sample files, is the responsibility of the ER/ES system operator.

Table 1. Files that are affected by 21 CFR Part 11

Data set	Description
Method (.xmt)	The method configuration is a protocol file in XML format defined by QIAGEN. The file contains the parameters for the electrophoresis run on the QIAxcel Advanced instrument.
Alignment marker (.xam)	The alignment marker is a file in XML format defined by QIAGEN which describes the fragments of an alignment marker.
Size marker (.xsm)	The size marker is a file in XML format which describes the fragments of a size marker. QIAGEN provides size marker files for all available QIAGEN size markers. Users can create and save their own size marker files by adding and defining their own size marker fragments.
Reference marker (.xrm)	The reference marker is a file in XML format. It can be saved by the user in order to reuse a size marker run for following sample runs and analysis.
Analysis profile (.xap)	The analysis profile is a file in XML format which contains the analysis parametrization for the basic analysis. A set of default analysis profiles is provided by QIAGEN with the system. Additional customized analysis profile files can be created and saved by the user.
Distribution profile (.xda)	The distribution profile is a file in XML format which contains the analysis parametrization for distribution analysis. A set of distribution profiles can be obtained from QIAGEN. Additional customized distribution profile files can be created and saved by the user.
Peak calling instruction (.xbp)	The peak calling instruction is a file in XML format which contains the analysis parametrization for peak calling analysis. A set of default peak calling instruction files is provided by QIAGEN with the system. Additional customized peak calling instruction files can be created and saved by the user.
Report/export profile (.xre)	The report/export profile is a file in XML format that contains the parametrization used for report generation. Additionally, the file contains the parameters that define which kind of files shall be generated for file export. A set of default report/export profile files is provided by QIAGEN with the system. Additional report/export profile files can be created and saved by the user.
Process profile (.xpp)	The process profile is a file in XML format that contains instructions for the experiment procedure and can be parametrized by the user in the experiment setup wizard. It can be saved by the user for reuse. It contains of at least one method, and, optionally, of an alignment marker, size marker, reference marker, analysis profile, distribution profile, peak calling instruction, and report/export profile.
	A set of default process profile files is provided by QIAGEN with the system. Additional process profile files can be created and saved by the user in the experiment setup wizard.

Data set	Description
Experiment file (.xdrx, .xrrx)	The experiment file contains of all parameters, runtime information, and raw data acquired during the electrophoresis of a single experiment. If analysis has been performed (analysis steps are optional), the analysis results and analysis parameters are also part of the file. After electrophoresis, the acquired raw data and related run information can no longer be modified. Analysis can be performed multiple times based on the raw data and the chosen analysis parameters (profiles). The experiment file always contains the results of the last performed analysis and the used profiles with all their parameters.
Report file (.pdf)	The report file is a readable file in PDF format optimized for printing that the user can opt to create after execution of an experiment. The file contains comprehensive data from the automated experiment procedure. The user can configure what shall be part of the report, e.g. electropherogram or gel images, analysis result tables, analysis parameters. Report configuration can be saved for reuse in a report/export profile.
Export file (.xml)	The export file in XML format is optimized for electronic data transfer or computational parsing, and can be created by the user after execution of an experiment. The file contains comprehensive data from the automated experiment, including analysis results. Raw data can be exported to separate files. If image files have been configured to be exported, the file names of the images are referenced in the export file. Export configuration can be saved for reuse together with report configuration in a report/export profile.
Image files (.png, .tiff, .jpeg)	The export function provides the option to export electropherogram and/or gel image files individually by the users need.

Compliance with 21 CFR Part 11 involves both technical (i.e. hardware and software) and procedural requirements. This Technical Information explains how the QIAxcel Advanced system contributes to fulfilling the technical requirements of 21 CFR Part 11.10: *Controls for closed systems.*

Examples of the procedural requirement of 21 CFR Part 11.10 that must also be fulfilled include: the training of users, the control of system documentation and the control of system access. Fulfilling procedural requirements involves the establishment of standard operating procedures (SOPs) which must be followed by users of the QIAxcel Advanced system. Depending on the specific requirements to be fulfilled, compliance is the responsibility of the company or laboratory operating the QIAxcel Advanced, QIAGEN, or both parties. The sections of 21 CFR Part 11.10 and how the QIAxcel Advanced, as a closed system, contributes to compliance with them are as follows.

Controls for Closed Systems – 21 CFR Part 11.10

Validation – 21 CFR Part 11.10 (a)

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

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. The procedures and controls also ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include:

This defines the need for validation of the electronic record system installed at the company or laboratory operating the QIAxcel Advanced system.

The QIAxcel Advanced system provides mechanisms to check the validity of electronic records. The electronic records enable the detection of unauthorized alterations. The software performs a checksum validation when such a file is loaded. The software presents an error when a modified or incomplete record is loaded.

The company or laboratory must validate the QIAxcel Advanced system as part of the electronic record system.

Readability – 21 CFR Part 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.

All files that are created or used by the QIAxcel Advanced system are listed in Table 1. These files are .xml files that can be viewed and printed via many text or word-processing programs.

Method files are created by QIAGEN only. User created profiles can be printed in pdf format. The software generates a report file in PDF format. An additional export file is provided in .xml format for electronic data processing.

Archived record protection – 21 CFR Part 11.10 (c)

Protection of records to enable their accurate and ready retrieval throughout the records retention period.

The QIAxcel Advanced system generates electronic records that do not expire and stay on the computer's file system until the user transfers these files to an external electronic archive. The transfer to an external electronic archive and the management of the electronic archive is under the responsibility and control of the company or laboratory. In addition, the QIAxcel Advanced system provides a function to delete user created profiles. The access to this function can be controlled in the user management.

System security – 21 CFR Part 11.10 (d)

Limit system access to authorized individuals.

User management of the QIAxcel Advanced system enables creation of user accounts based on roles. Access to the system is controlled by user login. QIAxcel Advanced users with "Routine" access can only run

experiments by using predefined process profiles, whereas users with "Advanced" access can define or modify process and all kind of analysis profiles. Users with "Administrator" access can change global software settings and manage user accounts. All changes to the user accounts are logged in the audit trail. It is the responsibility of the company or laboratory to limit access to the computer to authorized individuals.

The QIAxcel Advanced system automatically creates an audit trail that records the type of action, the user identification, and the date and time of actions that create or modify the configuration of the system. The audit trail records creation and modification of user accounts, user login and logout, the creation of an experiment, and the time of analysis and saving. Changes to values in profiles, e.g. analysis profiles, are not recorded. However, the experiment file always includes all analysis parameters that have been used to create the analysis results.

The audit trail is stored as a text file in the file system until the configured file size and file number is reached. The audit trail file enables the detection of unauthorized alterations. The software performs a checksum check at software start. The software presents an error when a modification of the audit trail file is detected or if the audit trail file is missing. The software automatically starts a new audit trail file in this case, starting the file with the error message. The archiving of audit trail data are under the responsibility and control of the company or laboratory.

The QIAxcel Advanced system performs checks to ensure that users run protocol files correctly. Only protocols provided by QIAGEN can be run on the system. The user is guided with step-by-step instructions during experiment setup. The system checks and validates the user input on the User Interface (UI). The user must confirm that he or she has followed the loading instruction before initiating an experiment. All input data is checked before the system starts an experiment. For experimental runs on a routine basis use the user role "Routine".

Access to software functions is based on a set of permissions. These permissions are related to different user roles. Only authorized users can add or delete files, setup and start experiments, change software settings, or create additional user accounts. It is the responsibility of the company or laboratory to assign the appropriate user role to each individual depending on the desired level of authorization. It is the ▷

Audit trail – 21 CFR Part 11.10 (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 available for agency review and copying.

Sequencing – 21 CFR Part 11.10 (f)

Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

Authority – 21 CFR Part 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.

responsibility of the company or laboratory to limit access to the computer to authorized individuals.

The content of experiment files is signed with a signature by the QIAxcel Advanced system. Any modification to the content or name of the file, including the signature itself, invalidates the experiment file.

Reports in PDF format are protected against modifications by using default security capabilities of the portable document format. The user is not able to modify the PDF files after they have been created. In addition, configuration files, protocol files, profile files, and electronic readable export files are protected by using a checksum to detect inappropriate modification. The checksum is an alpha-numerical value assigned to a file by the system and is based on the content of the file. The file is invalid if the checksum does not match the file's content or if it is missing. The QIAxcel Advanced system will show an error indicating an invalid checksum when the user tries to load an invalid file.

The QIAxcel Advanced system does not provide electronic signature functionality.

Location checks – 21 CFR Part 11.10 (h)

Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

The validity of the source of data for configuration data, protocol, and profile files is ensured by validating the checksum of the files. This ensures that all input data of an experiment (except sample ID definition) has been generated by a QIAGEN personnel or software and that the data have not been altered after generation.

Education/training – 21 CFR Part 11.10 (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.

QIAGEN supplies training with the initial installation of the QIAxcel Advanced instrument, and also provides additional trainings on request. In addition, user manuals and documentation are provided by QIAGEN. Establishing and maintaining the appropriate training level for QIAxcel Advanced users is the responsibility of the company or laboratory. The QIAxcel Advanced system supports fulfillment of this requirement by applying a role-based user management. The QIAxcel Advanced system does not provide electronic signature functionality.

Written policies – 21 CFR Part 11.10 (j)

The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

The company or laboratory operating the QIAxcel Advanced system is responsible for establishing the policies and procedures to support compliance with this regulation.

The QIAxcel Advanced system is delivered together with electronic user documentation that is associated with the specific version of the software. The manuals are provided in PDF as well as context sensitive help and cannot be changed by the user. The electronic user manual is installed with the software and can easily be reached via the help menu.

The distribution of the documentation to users of the QIAxcel Advanced system and version control of the documentation is the responsibility of the company or laboratory.

Summary

The sections of 21 CFR Part 11.10, their subjects, and how and by whom the subjects are handled are summarized in Table 2.

Table 2. Responsibilities of the Company/Laboratory and QIAGEN

Section	Subject	Laboratory Company	QIAGEN	Handled by
11.10 (a)	Validation	✓		Policies of the company or laboratory operating the QIAxcel Advanced system
11.10 (b)	Readability		✓	Existence of electronic records in human readable form that are viewable via many software programs
11.10 (c)	Archived	✓	✓	All electronic records are kept on the file system, until the user transfers them to an external electronic archive
11.10 (d)	System security	✓	✓	Control of access to the QIAxcel Advanced system through individual authentication
11.10 (e)	Audit trail	✓	✓	The system tracks changes in an audit trail. The creation of regular backups is under the responsibility and control of the company or laboratory
11.10 (f)	Sequencing	✓	✓	The system provides guidance and checks for setting up an experiment. Only QIAGEN protocols can be run. The user has to confirm the loading instruction
11.10 (g)	Authority	✓	✓	Control of access to the system by individual authentication.
11.10 (h)	Location checks	✓	✓	Configuration and protocols are checked by the system. The sample ID input and loading is under the responsibility and control of the company or laboratory
11.10 (i)	Education	✓	✓	Manuals and documentation are provided by QIAGEN. Establishing and maintaining the appropriate training level is the responsibility of the company or laboratory
11.10 (j)	Written policies	✓		Establishing and maintaining procedures to comply with this regulation is the responsibility of the company or laboratory
11.10 (k)	System documentation	✓	✓	QIAxcel Advanced system documentation cannot be changed by the user. The distribution of documentation to the users and version control of the documentation is the responsibility of the company or laboratory.

For up-to-date licensing information and product-specific disclaimers, see the respective QIAGEN kit handbook or user manual. QIAGEN kit handbooks and user manuals are available at www.qiagen.com or can be requested from QIAGEN Technical Services or your local distributor.

Ordering **www.qiagen.com/shop** | Technical Support **support.qiagen.com** | Website **www.qiagen.com**