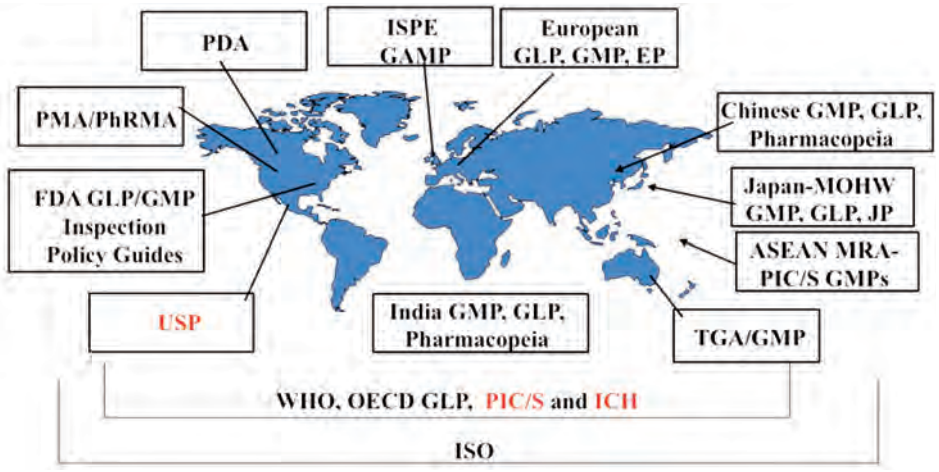
ANATOX
analytical solutions

AIQ-Tool Software

HPLC & GC Instrument Qualification

independent, reliable and neutral



The new OTS software for instrument qualification

AnaTox AIQ-Tool fills the gap regarding the independent certification and monitoring of all chromatographic instruments in the lab. The software provides full compliance with GLP, GMP and 21 CFR part 11 guidelines. The managing of the data of all instruments means that the status of each instrument is permanently available.
The tool helps to characterize the instruments by running system checks or full qualification procedures. It offers full access to installation, operational, performance and repair qualification procedures.
By using the AIQ tool, trained technicians or company employees are able to carry out the tests to verify functionality and performance of the chromatography systems. The software operates independently from the general laboratory chromatography data system (CDS), avoiding any interference with the validated environment.

USP 1058 and 4Q-Model, ISO 17025

Meets all specifications and requirements

For users in many countries, the qualification of analytical instruments is required by many national and international regulations like GLP or quality standards as ISO 17025. The goal is to acquire secure, reliable and accurate data from the instruments as well as to avoid out of specification situations. Finally it improves the instruments uptime.

For laboratories in the GxP environment, the specifications of the USP chapter <1058> became mandatory since 2008 [1] if USP monographs require using of qualified instruments for specific analysis or FDA inspectors expect instruments to be qualified when used for regulated testing. It leads to the often-applied process that the equipment should be routinely calibrated, inspected and checked according to a written program to ensure proper performance [2].

The categorization of equipment used in the laboratory in the categories A-C regulates the effort with respect to the qualification (Figure 2). All instrumental analysis devices are classified as category C instruments, including HPLC, GC and mass spectrometry.

The 4Q-Modell (Figure 1) describes and regulates the gradual approach of all steps of the qualification process. The process starts with the design qualification (DQ) where the user compares the requirements of the analytical method with the specification of the instrument manufacturer. Next, if the customer has ordered the optimal equipment it must be installed with a short operation check and the shipment with all options must be compared with the order. With an installation qualification (IQ), the status of all installed modules is fully documented and a simple analysis of a standard sample will be done, but no detailed evaluation of the analysis data is done.

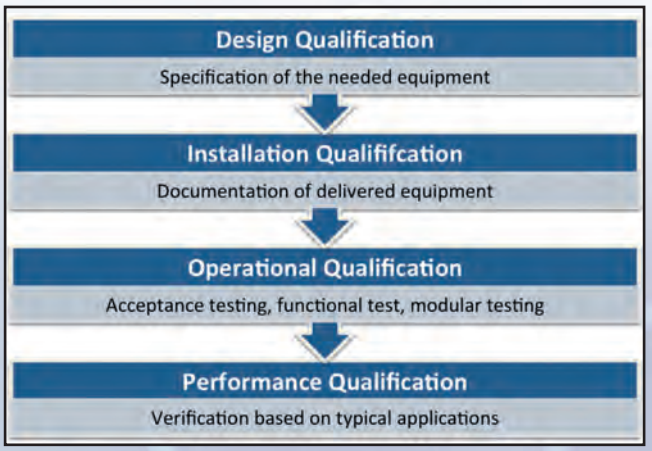


Figure 1: 4Q-Model according to USP 1058

At the next step, the equipment must be qualified according to the operational and performance specification OQ/PQ. During the OQ/PQ, the operability of the system according to the requirements of the DQ is checked against specific tests with traceable measurements. These measurements can be made by using specially calibrated measuring devices (traceable media) like thermometer but also by certified standards with certain properties.

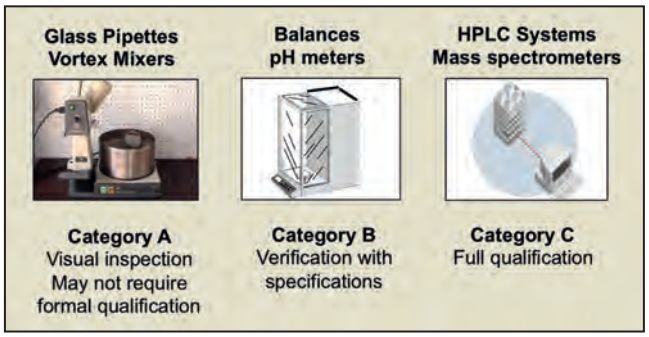


Figure 2: Categorization of lab equipment according to USP 1058

Validation and qualification of AIQ-Tool

Software validation is a requirement of the Quality System regulation. It applies to software used as components in medical devices, to software that is itself a medical device, and to software used in production of the device or in implementation of the device manufacturer's quality system [3]. Any software must be validated before its intended use. In March 1997, FDA issued 21 CFR part 11, which provides criteria for acceptance by FDA of electronic records, electronic signatures and handwritten signatures to electronic records as equivalent to paper records and handwritten signatures executed on paper. Re-examination after interpretation by FDA and industry lead to the current version from 2003. AnaTox has performed all steps of life cycle documentation of AIQ-Tool. This has included all steps of quality planning tasks (e.g. management plans for risk analysis and documentation, software quality assurance plan, problem reporting and resolution). Furthermore the software requirement specification documentation was created and used as a guide for validation and verification of AIQ-Tool. These activities have led to an extensive documentation that all customers can be provided to allow AIQ-Tool as a new standard in the company.

For labs that want use a neutral solution for qualification

Qualification independent from Manufacturer

With the publication and release of the final version of the USP chapter <1058> many discussions about instrument qualification have stopped. It clarified a lot of issues by formalizing the 4Q model for commercial instruments with no or less significant customization.
The qualification of equipment is not a single event. It starts typically with the definition of the product or project and ends with the system retirement. The qualification must be done independent from the specific application and can often only be verified with specifications for the complete instrument with the corresponding accessories.

Instruments become comparable

Neither USP chapters <1058 or 621 [4]> nor the monographs for many API (USP, EP) describe the use of an instrument from a specific manufacturer. In addition the quality and specification of analytical instruments became comparable in the last years. Therefore every manufacturer or vendor is admitted to be proofed by DQ if his instrument fulfils the requirements of the specific monograph or of the chapters of the pharmacopeia's for chromatographic determinations (e.g. USP <621>).
If the customer applies and uses the first step of the 4Q model - the Design Qualification - it would lead to a specification for an analytical instrument that meets the specification of several manufacturers. As an example, if looking at the monograph for paracetamol [5] for the assay determination as well as for detecting related substances, liquid chromatography with UV-detection is required. That allows the usage of any manufacturer of HPLC systems that fulfills the specification. The regulations and requirements lead to comparable setups and specifications for the instruments.

Qualifications manufacturer specific?

Every manufacturer and/or vendor has started the creation of qualification documents and procedures according to the 4Q-model after release of chapter <1058> if not already done. Therefore it was not unusual in the laboratories that different service engineers have evaluated similar devices from different manufacturers with different procedures. Until now, there is no harmonization of procedures and specifications for comparable instruments.
The aim of running analytical instrument qualification is to provide proof of system suitability for the intended use. If successfully completed any method validation can be started. When the method validation process is finished, any frequent system suitability test will verify that the system performs according to the analytical expectations (PQ). With quality control checks, the accuracy of sample analysis will be verified. The analytical data quality is only given if all these components fulfil the expected limits.Taking the components of analytical data quality (see figure 3) into account, the instrument qualification becomes the basis of all.

Easy adaption of in-house procedures

Differing from recommendations of many manufacturers, customers want to adapt a test due to their specific needs and applications. This is often not possible. AIQ-Tool provides the capability to select the test according to the needs or to implement a new test-setup. For example, the test of oven stability of column compartments works by reading the internal temperature and comparing this to a traceable media. Some customer wants to expand the time of acquiring data or only to read and evaluate data from the traceable media. This can easily adapted with AIQ-Tool.

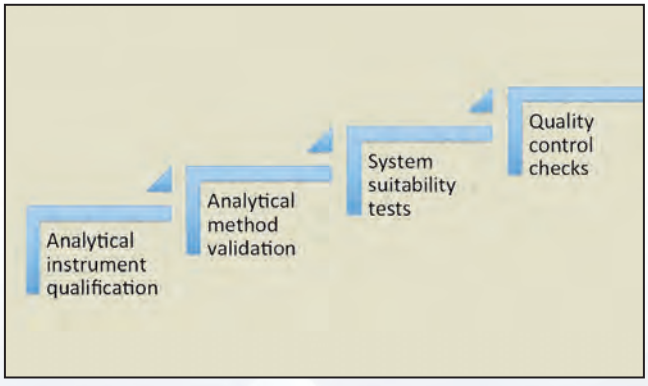


Figure 3: Security of analytical data quality

Harmonization of qualifications by AIQ-Tool

The AIQ-Tool is a manufacturer independent concept of the qualification process. The procedures are typical and well known to characterize analytical chromatographic instruments. It evaluates all requirements resulting from USP chapter <621> for qualitative and quantitative determinations by chromatography. It uses traceable media like calibrated thermometers and certified standards. In principle,

each user can perform the qualification itself if he uses the above-mentioned appropriate validated media or tests to qualify the technical equipment with independent and traceable procedures.

Data Acquisition by AIQ-Tool

The new driver concept of AIQ-Tool uses the direct control of the connected instrument. It allows the data acquisition without the CDS of the user/customer. It secures that the qualification has no influence on the qualified environment in the lab. All acquired data are stored in the database and cannot be manipulated by external access.

Data evaluation according to validated calculations

The acquired data will be processed by AIQ-Tool using calculations that are referenced and validated. One example is the evaluation of detector noise, wander and drift. The procedure is based on ASTM standard 685-93 [6] and is widely used by many manufacturers for evaluation of their systems. When performing the operational qualification for AIQ-Tool, reference data will be used for the evaluation of all implemented calculation processes. These data are available on request for every customer by export out of AIQ-Tool to check with their own validated programs.

Typical chromatographic equipment (LC, GC, MS)

Traceability of data according to own qualification formalities

Data can be self administered

One of the FDA GMP requirements is the signing of the analytical results by the analysts, they having the ultimate responsibility that the used instruments and computer systems are qualified and validated. This fact of ultimate responsibility for instrument qualification does not mean that they have to conduct all qualification activities. If the users are trained and can obtain calibrated tools and standards they can run the qualification procedures themselves.
Some activities e.g. the IQs and OQs can be delegated to the instrument vendors or to 3rd party organizations. An advantage of delegating the activities is that the external personal is trained, experienced and will bring all necessary calibrated tools that are required. If the customers use calibrated tools and standards they can run the qualification procedures themselves.
An additional requirement for group C instruments equipped with computer systems is the data handling. This field includes the regulations for back-up, the security setup and system administration.
The overview of the AIQ-Tool software program structure is shown in Figure 4. All functions and program modules are equipped with user rights. The user rights will be configured in the central user management & administration module of the software. That opens several options of using the qualification software.

Using AIQ-Tool internally

By using AIQ-Tool fully internally at the customer site, the analyst and/or user is trained and certified by AnaTox. The customer can use all functions and features. When creating users it can be set for those operators that can run qualification but only have access to the actual report. No access to reports of other systems or older reports in the lab is granted. In addition, users can be created that only have access to manage reports but can not run qualification because of missing training and certificates.
If used fully internally, the customer can run qualifications as needed. The advantage is a very fast access for example in case of repair. Besides, it opens best economical managing of the capabilities of the personnel and equipment. AIQ-Tool can be used for all systems and modules that must be qualified in the whole laboratory or company.
It allows the customer a fully digital managing of all reports and configuration data. Any data that was not printed with the first report e.g. an audit trail protocol can be generated later. Using internaly for example on a laptop allows the customer to archive the complete setup of the computer system and for all instruments.
If installed on each workstation and not on a portable computer the customer can back-up each database. This feature is useful if data should be separated between the labs. By using this feature every lab can use its own database and can archive the data itself. When running the next qualification the database of the lab can be restored in AIQ-Tool and the new data will be added until next back-up. As a disadvantage appears that each installation must be qualified itself.

Performing qualifications by external personnel

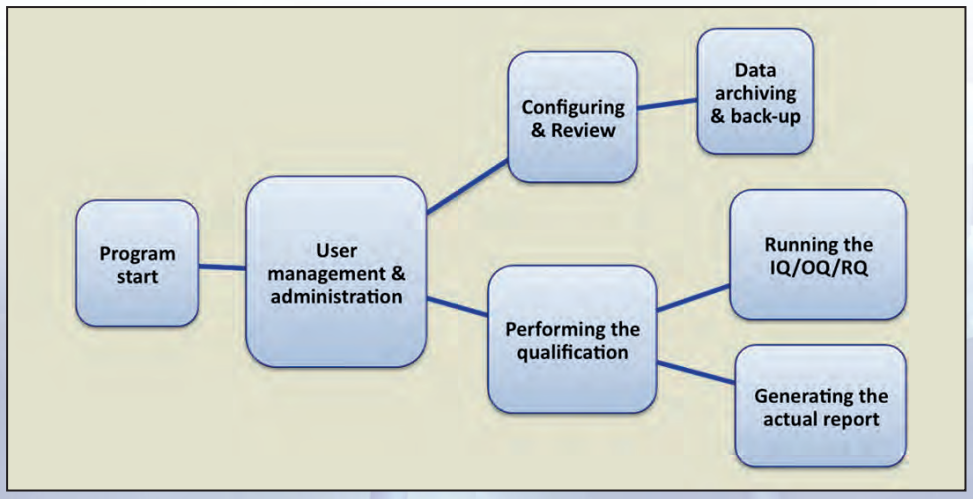


Figure 4: AIQ-Program structure regarding the access to features

If the qualifications should be delegated to external vendors AIQ-Tool supports the data integrity by its program structure. The external technician will provide all necessary calibrated tools, no effort for the customer to buy and keep it calibrated. All certificates are valid for any qualification.
The external authority is trained and certified to run

the qualification, no own personnel capacities are needed. If the activities are scheduled the downtime of the system/s is/are minimized. One advantage for the customer is that the maintenance of the systems can be performed just before the qualification. The customer has several options regarding the data handling. If the external vendor performs the qualification and prints the report at the end no additional effort is necessary for archiving and back-up the data. For any issue related to AIQ-Tool the external vendor is responsible, e.g. updates. An alternative is the installation of AIQ-Tool at the customer site and creating a lab user with permission only to manage reports and data (for archiving and back-ups) and granting administration rights only to the external authority. One additional option is to install AIQ-Tool with full rights and only grant the permission to run qualifications by the external vendor. All setups are used to secure data integrity and give the highest flexibility to use AIQ-Tool for Qualification.

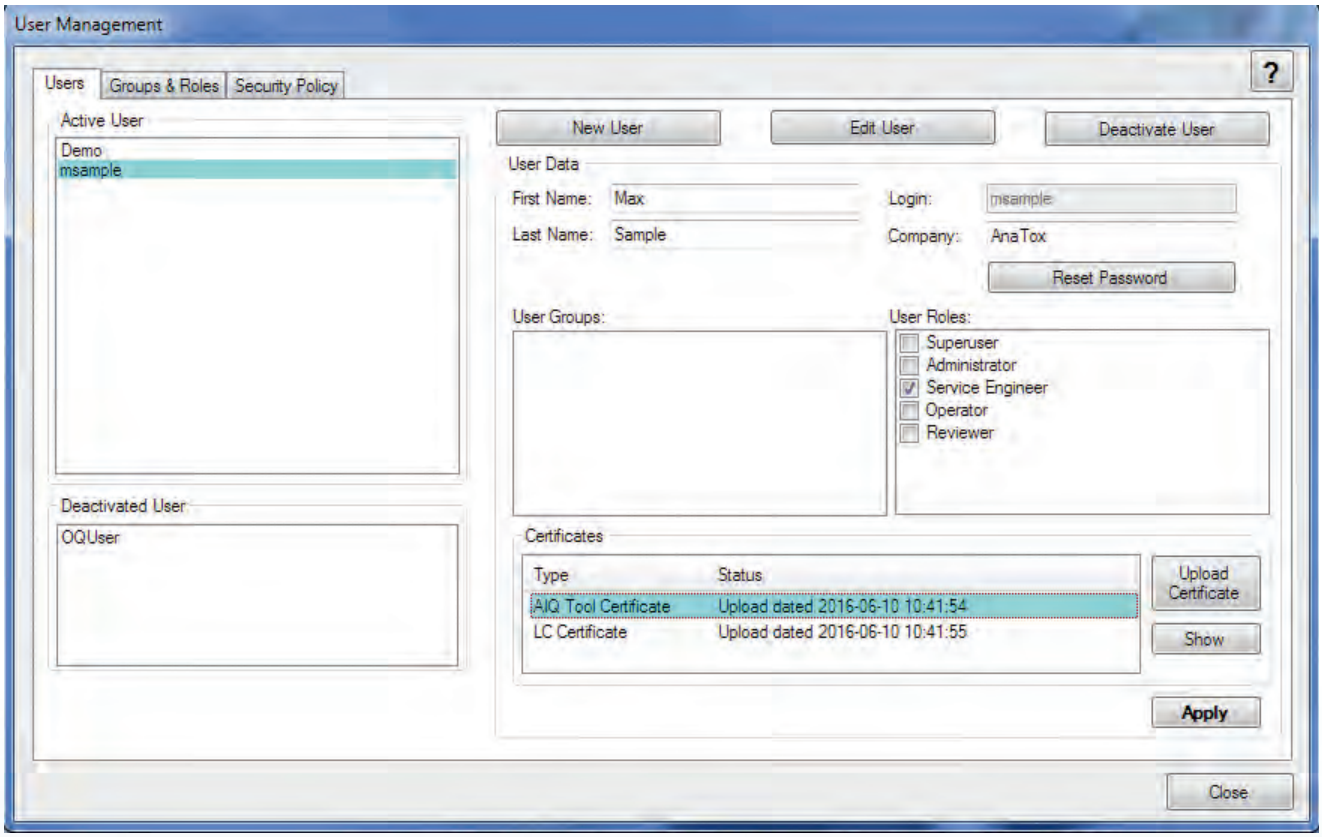


Figure 5: Setup of an service engineer as an external operator

Easy handling of the tool and free of manipulations

Automated Running of the Qualification

When starting the AIQ-Tool for the first time, the program initialises the Audit Trail log and prompts the user/administrator to generate users and operators and grant them their user rights. The installation and

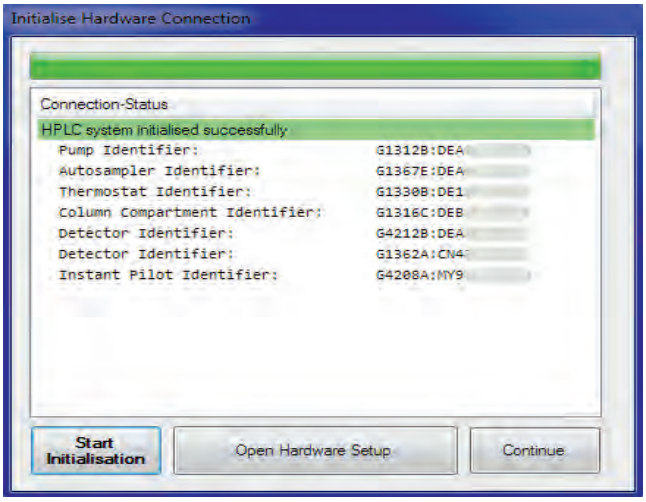


Figure 6: Initialisation of the instrument

operational qualification procedures for AIQ-Tool itself can be run immediately before first use.
Next the IP address of the instrument must be entered to establish the connection. This could be saved for frequent requalification. By starting the connection process with the instrument, all available data will be read out to check for available modules. All available modules will be registered (see Figure 6) independent if they should be qualified or not. This will be printed in the audit trail log. In some cases, mobile controllers are connected. These controllers will be detected by AIQ-Tool and blocked after start of the qualification procedure. It is not possible to alter any parameters during the procedure. This will ensure that the parameters used for qualification cannot be manipulated. The same happens with the access of the CDS to the module.

Qualification status of the instrument

AIQ-Tool checks the actual qualification status of each module when reading the configuration. It compares the status of the last qualification regarding the composition of the instruments, e.g. have new modules been added or exchanged. In case that the date of the last qualification is not identical for each module of the system, AIQ-Tool allows the qualification of parts of the instrument. This is very useful if you must qualify a module e.g. a gradient pump and the only available detector is a refraction index detector. In those cases an external second detector is necessary to run the gradient test. This detector should already be qualified and you can integrate this as a second detector or it can be qualified during the actual procedure (see Figure 7).
In case of a repair qualification, the actual status of the modules of this instrument will be checked to ensure that a qualified instrument will be used to qualify the repaired instrument.

Automatic selection of mandatory tests

Each module will be classified according to its features and options. For example, as seen in Figure 7 the binary pump was recognized as a high pres-

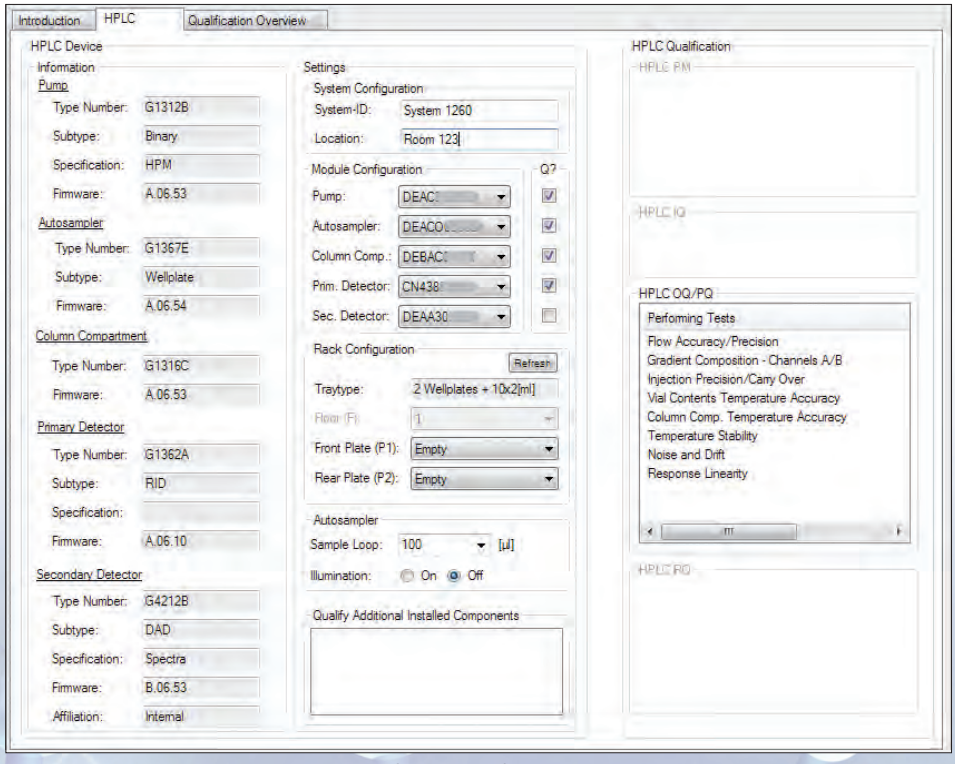


Figure 7: Setup the instrument for qualification

sure mixing gradient pump (HPM). Therefore only the corresponding gradient test for channels A and B was selected. In case of a quaternary low pressure mixing gradient pump (LPM) two gradient tests would be mandatory for channels A und B as well as for channels C and D.
The configuration read out during initialisation will be used to generate the list of tests to be run. The second detector (see Figure 7) will not be qualified during this procedure because it was already done earlier and the qualification certificate can be used for verification as a traceable media. The aim of the tests and their limits are discussed in terms of their specificity and target between operator and customer before the start. The list of mandatory tests cannot be edited before or during an operational qualification.

Requalification after repair

If one of the modules was repaired after successful completion of an OQ/PQ, the user can perform the requalification of the repaired module. In case of a "repair" qualification AIQ-Tool checks the qualification status of each module. It prompts the operator to select one of the typical repair activities (see Figure 8) and AIQ-Tool will automatically select the mandatory test/s for requalification. If only one of the typical OQ tests is mandatory, the operator can select all tests to run the requalification for better comparison to the OQ results.

Test limits

Typically in AIQ-Tool, limits for all tests were implemented according to the recommendations of the manufacturer/s. The operator can edit these limits (see Figure 9) before starting the procedure to adapt it to the requirements of the intended use in the lab or the method. By printing the qualification plan, the limits will be adopted and an actual printout for this qualification will be generated for documentation.

Prerequisites

When all modules with all options for the qualification are selected, AIQ-Tool automatically selects the mandatory tests for the qualification procedure and sorts it for best performance. This will ensure that no test will be forgotten and no test can be deselected. Only running of all tests will ensure the successful completion of the qualification procedure.

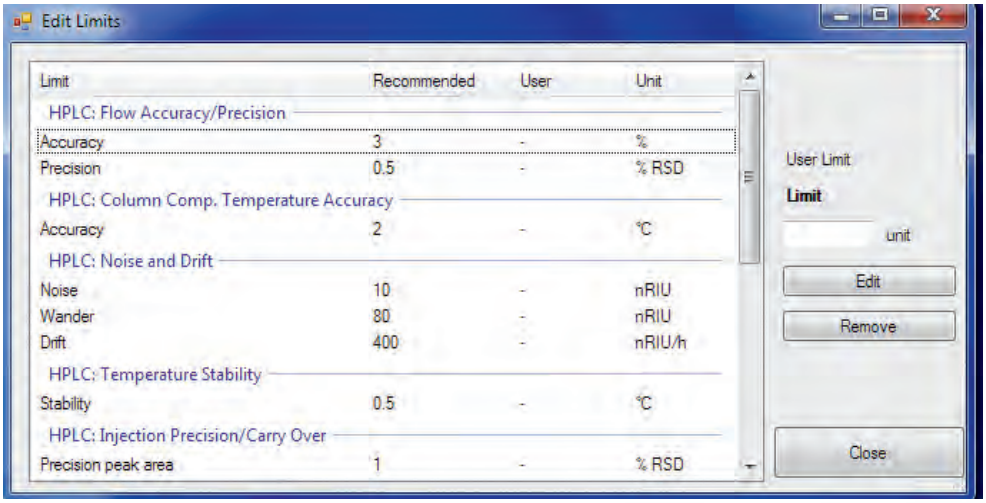


Figure 9: Editing the qualification limits

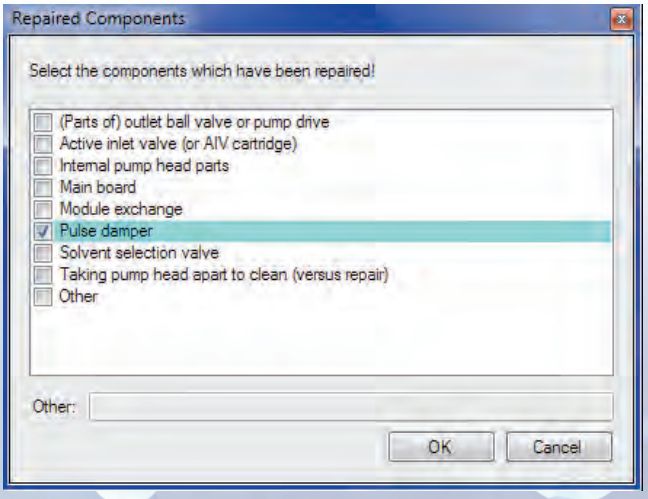


Figure 8: Selecting the repaired component of a pump

In some cases when modules should be qualified with options that cannot be detected by AIQ-Tool, the operator can manually select the option from the menu. One example is the qualification of a thermostated flow cell of a HPLC fluorescence detector. The corresponding test/s will be added automatically to the procedure for the selected option.
After selection of the modules of the instrument the list of prerequisites will be generated for qualification. During the qualification setup it will be checked that all required data of the prerequisites were entered to run the procedure.

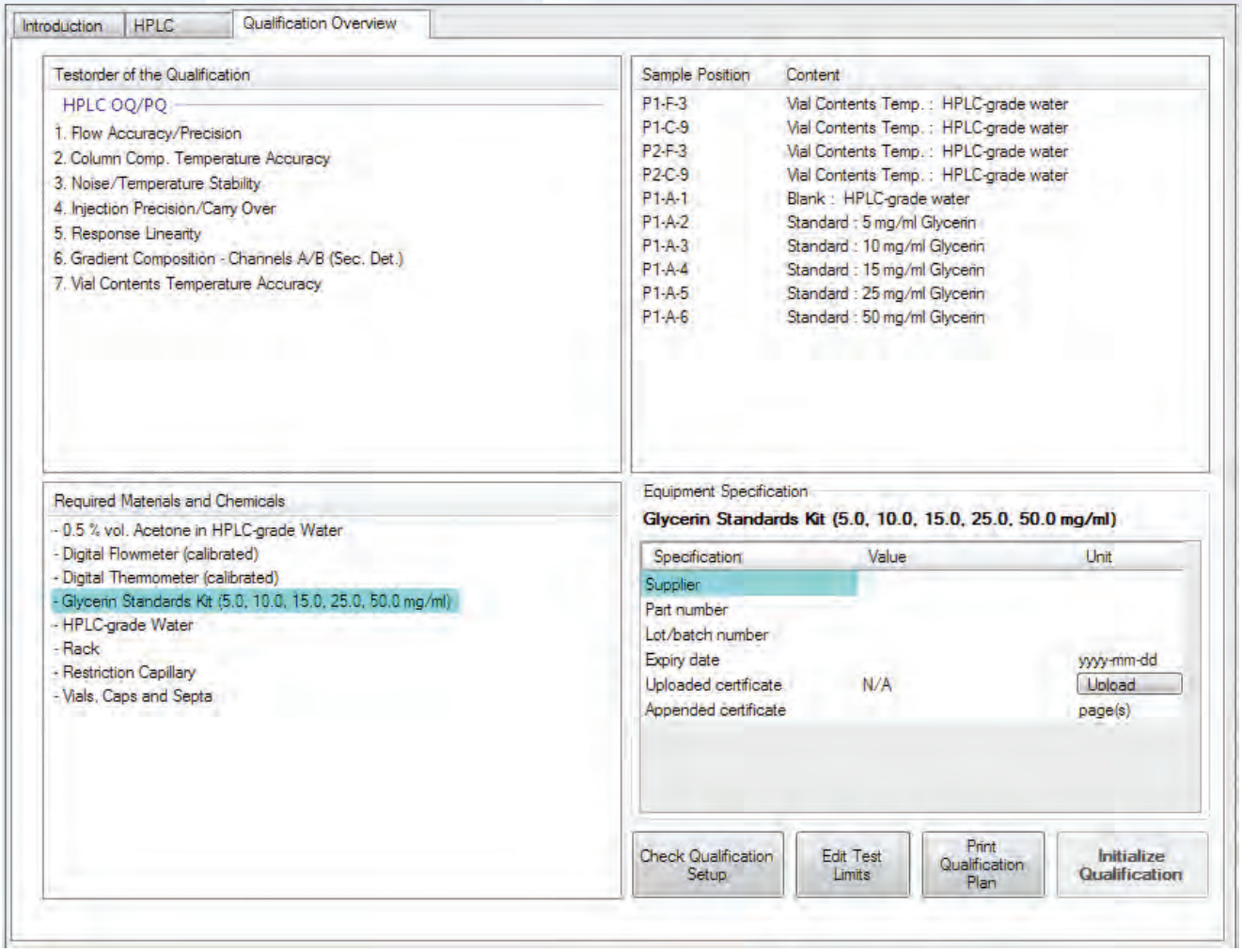


Figure 10: Qualification overview and editing data of prerequisites

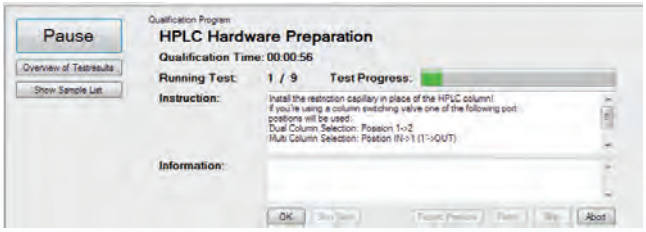


Figure 11: Automatic preconditioning of the hardware

Automatic preconditioning

The procedure can only be started after all data of the prerequisites have been entered (see Figure 10). The operator will be guided step by step through the procedure by instructions. A lot of information will be available during the procedure, e.g. pressure of the HPLC pump or temperature of the injector.
AIQ-Tool will automatically run several preparatory steps with the instrument to ensure that the instrument is properly conditioned. Many recommendations of the manufacturer and a lot of experience are implemented, for example to make sure that the deuterium lamp of an UV detector was switched on at least 1h before starting the first test. Furthermore every channel of the HPLC pump will be automatically flushed to ensure that the eluents for qualification will flush out any residues of preliminary solvents. Many parameters like "pump ripple" will be checked before running the related test of the module.

Running the qualification procedure

When starting the procedure, the operator can print the sample list as shown in Figure 11 and sort the samples depending on the used rack and standards. This is necessary to complete the preparation of the qualification procedure.
When the preparation has finished, AIQ-Tool sends all necessary parameters to the instruments and checks the status of all modules before starting a test. For example to ensure that the pump is delivering the correct flow, the flow test of a HPLC pump is only started when the ripple shows values

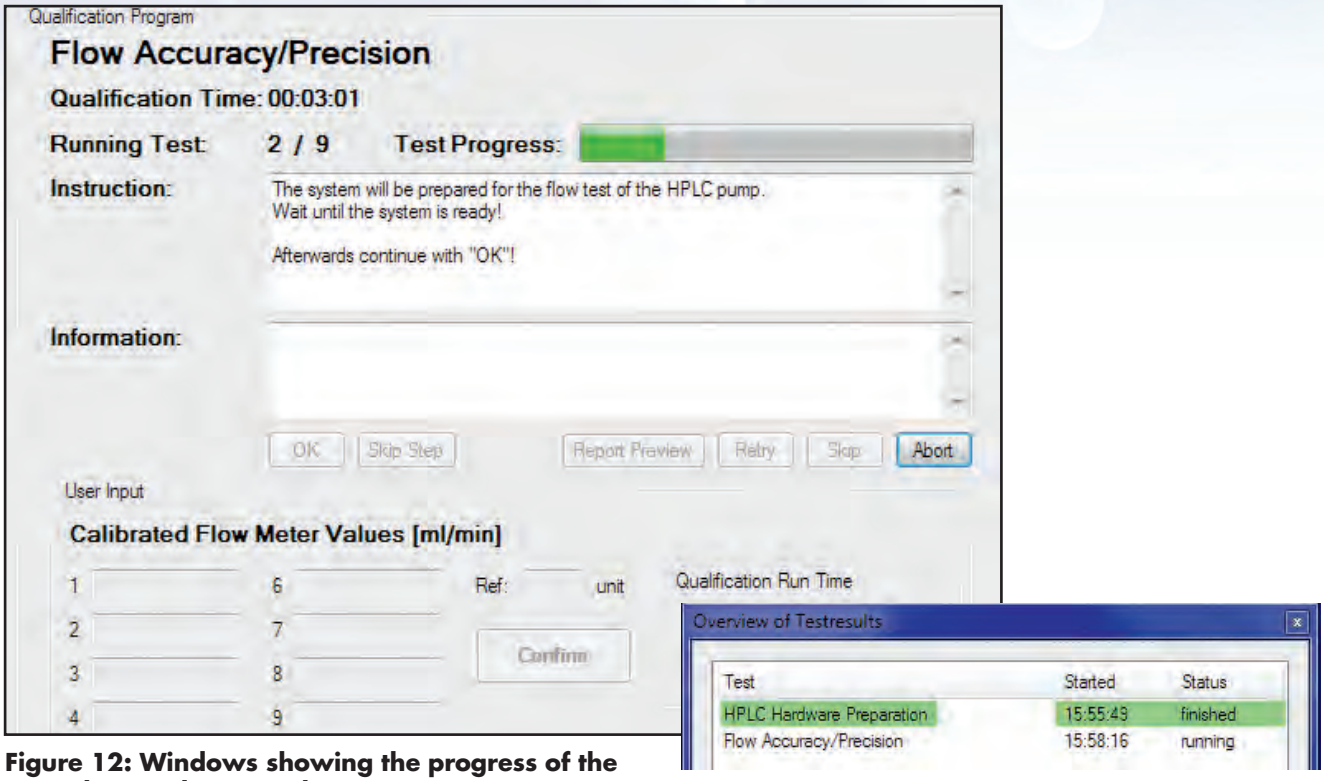


Figure 12: Windows showing the progress of the procedure and test results

in-between ±1%. During the whole procedure a permanent monitoring of all parameters by AIQ-Tool ensures that all parameters keep constant. An online plot shows the real signal coming from the detector. Many of the tests run fully automatically. If tests require an external trace, e.g. a thermometer, the operator will be prompted to install the measuring device. When the media are properly installed the operator can enter the requested data to finish the test. Each data and the time of entering the data will be logged in the audit trail.
For data processing a separate "Integrator" as well as functions for the evaluation of spectra and much more were integrated to reprocess the raw data without CDS. Each test will directly be evaluated after finishing data acquisition. The test result will be printed on the screen. When the status shows a "passed" the next test will be loaded and started if the instrument is ready. If the test fails the procedure stops, the operator can rerun the test after entering a comment as an assumption as to why the test failed or what was done for correction. In case of an error, the procedure will be terminated.

Data acquisition of non controlled modules

AIQ-Tool also supports the qualification of chromatography systems that are not directly controlled. A lot of special detectors from many manufacturers possess an analogous output. In those cases, the customer can connect an A/D converter for direct data acquisition. The operator must transfer the chromatographic parameters shown by AIQ-Tool to the modules and start the corresponding run. The signal from the external module/detector will be converted in that way that data storing and processing is done by AIQ-Tool.

Qualification by data import

Every vendor of CDSs has implemented the option to export raw data as an AIA/ANDI export. Typically the exported raw data are stored in "common data format" (CDF). This format is well known, documented and allows storing of scalar and multi-dimensional data in a platform-independent way. By using this way it is possible to run "qualification methods" and acquire the corresponding data to export for evaluation.
AIQ-Tool is ready to import, read and process these data inclusive the time stamp data. First, the type of module/s that should be qualified must be selected and the limits must be entered. Then the operator can run the methods from the lab-CDS and import the resulting raw data into AIQ-Tool for reprocessing and evaluation. The documentation of all serial number and batch numbers remains identical to the standard procedure. The report at the end will be generated on the basis of the imported data.

Paperless reporting, if you want

Full documentation fully digital

When AIQ-Tool is to be used, the training of the operator is mandatory to make sure that the procedure/s is/are performed correctly. Every operator will be trained by AnaTox to get a certificate that can be uploaded into the database and linked to this user (see Figure 5). All certificates will show the training history and allows a verification of the actual training status of each operator (only for administrators). When uploading the certificates to all users/operators it simplifies the usage of AIQ-Tool independent from the operator. Every time a qualification is started, it will be checked if a certificate is available. If yes, the corresponding certificate will be automatically loaded with the operator login and used/printed within the report.
The qualification procedure cannot be started before all necessary data of the prerequisites have been entered (see Figure 10). By selecting each prerequisite from the list in the left bottom window, the operator can enter the corresponding data in the right bottom window. For example, the operator must enter the order number and the batch number for the caffeine standard that should be used. Additionally it is possible to upload the scanned certificate as a pdf-file. The data of the caffeine standard will be printed on each test where it was used and the certificate will be printed as an appendix at the end of the report.
If you want to have all batch numbers and certificates completely digitalized for digital printing of the report they must be entered and uploaded in advance. If this is not possible, the operator can specify the number of printed pages that will be added to the report as an appendix.

Reporting

The main result of a qualification is the qualification report. The database shows all finished qualification procedures. Every report can be printed from the database, but each printing will increase the printing ID. Therefore in case of inspection, the printed copy of the report must have the same ID as in the database.
Every report also lists all failed runs in its full version. This can be compared with the data from the audit trail protocol. The report is only valid if all entries of the audit trail and the generated report are identical.
As long as always the „same database" is used, a complete digital history of the system/all systems can be established thus. The data are regularly archived and are highly secure in terms of a complete traceability and documentation of qualifying history.
AIQ-Tool provides full support of reporting capabilities to meet the requirements of the current good manufacturing practices/compliance regarding 21 CFR Part 11 [7]. This includes the creation of accurate and complete copies of records suitable for inspection and review as well as their protection for retrieval throughout the records retention period. The limited access to authorized individuals is also implemented as well as the computer generated, time-stamped audit trails. The authority checks will ensure that only authorized individuals can use the system, access the operation, sign a record or alter a record.

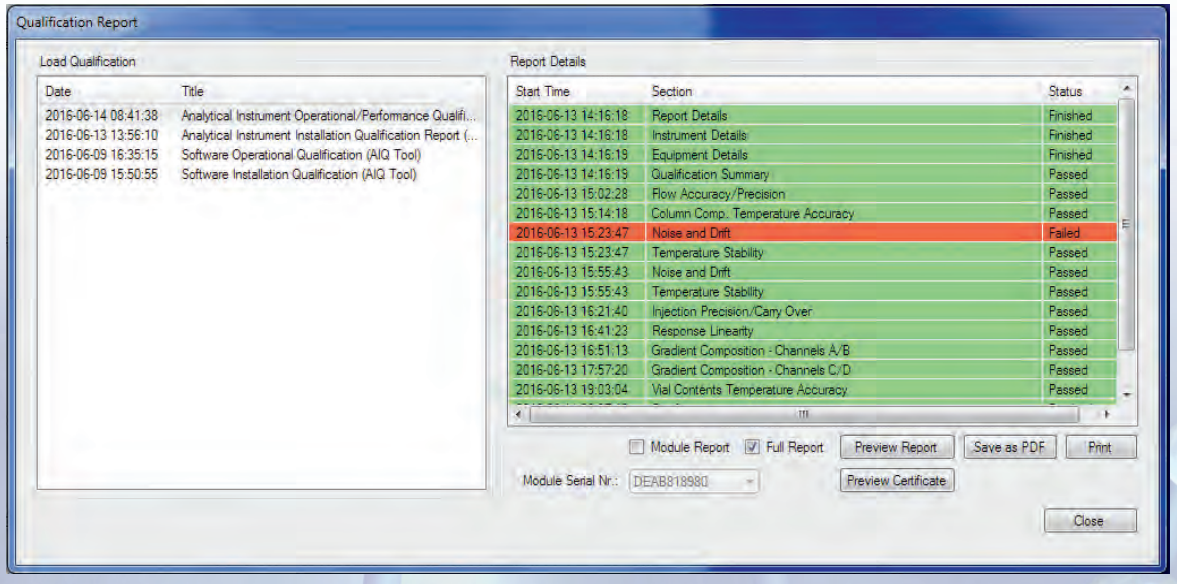


Figure 13: Selecting reports for printing and inspection

Maximum functionality, maximum flexibility

Complete solution

The AnaTox AIQ-Tool is a powerful tool for qualification of HPLC, GC and/or MS systems.
With this software, it is almost impossible to manipulate processes and measurements. Through the almost fully automated process, a high reproducibility is guaranteed regardless of the operators. Automatic documentation of all processes and results secures highest available traceability. Here the AIQ-Tool is setting new standards of qualifying hardware independently from the manufacturer.

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For more information

For more information about this or other products, please visit our web site at: **www.anatox.de**

Product information
P-1000094 – AIQ-Tool for HPLC/GC/MS
Software to qualify chromatography systems supporting IQ/OQ/PQ/RQ

Trebuser Str. 47, H9
15517 Fuerstenwalde, Germany

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FON: +49 3361 3698950
FAX: +49 3361 3695955

ANATOX
analytical solutions