Agilent ChemStation Plus

July 2004

Specifications

General Description

This document provides specifications for Agilent ChemStore C/S, Agilent ChemStation Plus Security Pack, Agilent ChemAccess C/S Agilent ChemStation Plus Method Validation Pack, which are part of the Agilent ChemStation Plus family. With the Agilent ChemStation Plus family you need to purchase only the features you require. This can be the fully featured software package for the most advanced capabilities, or you can exclude features that you may not want now, and add them later as your needs change.

The Agilent ChemStation Plus software package currently consists of the modules below.

Agilent ChemStation for GC, LC, LC/MSD, CE, UV-visible and A/D systems—instrument control, data evaluation systems. Detailed specifications are available in the Agilent ChemStation Specifications (Agilent publication number 5988-9925EN).

Agilent ChemStore C/S—data organizing and storage module that provides a scalable in-process chromatographic data organization system for Agilent ChemStations (pages 2–20).

Agilent ChemAccess C/S—remote access module that provides a laboratory-wide remote status and control client/server data system for networked Agilent ChemStations (pages 21–23).

Agilent ChemStation Plus Security Pack—designed to support the requirements of 21 CFR Part 11. It uses a relational database based on the ChemStore C/S database for secure result data storage, data review and electronically signing off runs (pages 24–38).

Agilent ChemStation Plus Method Validation Pack—advanced statistics module to calculate the quality of analytical results including configuration, design and execution of method development and method validation experiments. It provides an automated printout of a complete method validation report as requested by ICH and Pharmacopoeia guidelines. All validation data are stored with versions in a built-in relational database for full data security and data integrity and to support FDA's 21 CFR Part 11 (pages 39–67).

Agilent Technologies

1. Agilent ChemStore C/S

What's New?

With the latest revision users can benefit of new functionality in many areas as listed below.

Workflow

- Up to three configurable levels of approval linked to separate user privileges (see *Agilent ChemStation Plus Security Pack – Electronic signatures and password settings* on page 33)
- Optional locking of runs after approval to prevent them from further modification (see *Agilent ChemStation Plus Security Pack – Electronic signatures and password settings* on page 33)
- New chromatogram viewer providing dynamic zooming and rescaling capabilities (see *Agilent ChemStore C/S – User Interface* on page 15)
- Direct Read-access to ChemStation Method (see *Agilent ChemStation Plus Security Pack – Audit Trails and Change Documentation* on page 36)
- Variables in advanced queries for operator names and dates (see *Agilent ChemStore C/S – Working with Agilent ChemStore C/S* on page 10)
- New database field for area% results from ChemStation

Reporting

- Powerful custom calculator for advanced calculations, reporting and charting of calculation results, based on fully versioned calculation templates (see *ChemStore C/S – Working with Agilent ChemStore C/S*, *Custom calculations* on page 12)
- Optional peak performance calculation per-run or sequence line (see *ChemStore C/S – Reporting* on page 14)

Open system connectivity

- File-less LIMS interface (see *ChemStore C/S – LIMS Connectivity* on page 18)

Administration

- Email notification enhancements (see *Agilent ChemStation Plus Security Pack — E-Mail Notification* on page 37)
- Configurable command line access (see *ChemStation Plus Security Pack — User Management and Application Security* on page 28)
- Support for Windows XP Professional Workstation
- Drop of support for Windows NT Workstation
- Support for Oracle 9i

Product Description

Agilent ChemStore C/S is a scalable in-process chromatographic database for Agilent ChemStations. It provides a means to easily organize, review and approve analytical data based on study and sample information. Agilent ChemStore C/S supports the users' data review process offering statistically result summaries, flexible control charts, cross-sample reports and documented data archiving and restoring. These services also aid users in doing on-going system suitability testing. The Agilent ChemStore C/S server database can be used as a single place for data storage for all analytical data including methods, sequences and the raw data. This data storage also satisfies the requirements for data handling in a regulated environment including the detailed requirements of the U.S. food and drug administration for electronic records and electronic signatures, known as 21 CFR Part 11.

Agilent ChemStore C/S is available in two different configurations:

- **Agilent ChemStore C/S standalone database**
  This provides a low cost, easy-to-use, entry-level database module which integrates with a single Agilent ChemStation workstation.Very limited maintenance support is required and any user with advanced knowledge of the Windows XP or Windows 2000 operation system functionality for backup and administration can maintain it. This entry-level database module allows for storage of all raw and meta data in single database file to ensure full data integrity. The file format adheres to a common standard, which is used by many other applications, for example, MS Access.

- **Agilent ChemStore C/S server Oracle® database client/server system**
  This client/server system is based on an Oracle database running on a Windows 2000 server together with multiple Agilent ChemStations and/or Agilent ChemStore C/S review clients. It provides enhanced data security and data integrity, distributed processing, as well as the ability to store raw data, methods and sequence files within the database. This configuration reflects best the

regulatory needs for electronic records and ensures full data integrity and traceability.

Based on standard database features, Agilent ChemStore C/S offers functionality which focuses on the user's needs for fast, secure and traceable handling of chromatographic data:

- User-defined or automated transfer of selected data from the Agilent ChemStation into the Agilent ChemStore C/S database.
- Define, edit and manage "studies" as the underlying data storage format.
- Manage or restrict data access in studies by assigning study access only to authorized users.
- Create database queries graphically without the need for any knowledge of the SQL language.
- Review entire sets of data across instruments and studies, that several sequences in a fast and easy manner.
- Create additional filters and selection criteria to produce adequate subsets of the study in order to best sort the data and optimize the performance.
- Complete audit traceability by individual log-ins and complete documentation within the database including authorization failures.
- Security check of all files that have been transferred over the network from the ChemStation application to the ChemStore database application and back. Whenever a corruption of the datafile is detected, the user receives an error message and the file is no longer available for modifications.
- Approve or reject runs after reviewing, following the rules for electronic signature.
- Ability to flag an arbitary set of samples for reprocessing, and to initiate batch reprocessing of those samples on any Agilent ChemStation in a C/S network.
- Custom fields—User specified additional information fields with each set of results ("run") to hold values not measured by the Agilent ChemStation (for example, weights, pH, etc.) that can be used for later queries, reports or charts.
- Flexibility in scaling and labeling control chart data.
- Simple user-defined calculations for control charts and reports.
- User-controlled fast and easy data export to other applications such as MS Excel®.
- Powerful and intuitive report generator based on MS Access runtime including most commonly used report templates.
- Architecture allows for off-line review. Can be installed as a data review client running on a separate PC without needing the Agilent ChemStation software.
- Data from non-Agilent chromatography systems may be included via the Agilent ChemStation AIA import capability.
- Agilent ChemStore C/S offers the possibility to start with an entry level solution, and to then upgrade when the data processing needs increase. Laboratories can easily upgrade from one or more entry-level standalone systems to an Agilent ChemStore C/S server Oracle database client/server system. Previously stored data in the entry-level databases can be easily migrated to the new server database. The user interface does not change, except that some additional items are available for administrators.
- A built-in archive/delete tool allows for easy data transfer to other disks and or media to free up database space while keeping a complete audit-trail of all archiving and delete operations.
- Automatic archiving based on a set of configurable archive queries for easy database maintenance and administration.
- Open system connectivity using XML (Extensible Markup Language) for easy data exchange with other applications.
- Advanced email notification feature (C/S only). See page 37 for details.

1. Agilent ChemStore C/S standalone

Hardware requirements

The following list shows the minimum hardware requirements for this application:

- 600-MHz Pentium III (Pentium IV recommend)
- 4 GByte of free hard disk space
- 128 MB RAM for single ChemStation instrument. 256 MB is recommended for best performance, for Windows XP the minimum requirement is 256 MB.
- 256 MB RAM for two ChemStation instruments (512 MB or more is recommended for best performance)
- Display: 1024 ∞ 768, small fonts, 65-thousand colors

Software requirements

The following list shows the minimum software requirements for this application:

- Windows 2000 Professional with Service Pack 4 or Windows XP Professional Service Pack 1a
- Agilent ChemStation revision A.10.01 or later
- Microsoft Internet Explorer 5.5 or later
- Microsoft data access components (MDAC) 2.8 will be installed on your system. If you already use a later version of MDAC, or for compatibility reasons require a previous ver sion, please contact your Agilent support representative for compatibility information.
- A local or network printer must be installed and configured.

Hardware considerations

Disk space requirements depend on several factors, such as:

- number of runs and compounds,
- technique (3D data requires more disk space than 2D data)
- Agilent ChemStation report style
- the “Store in Addition” settings of the study to which the run is assigned, (see table 4 on page 7), and
- use of custom fields
- database backup requirements

Typical runs use approximately 10 KB for a short report with four peaks, and use up to 300 KB per run for an extended performance report with 20 peaks. Table 1 helps calculate the amount of hard disk space requirements. Additional information on this topic may be found in the *Agilent ChemStore C/S Installation* manual and the *Concepts Guide*.

Note:
The standalone database size is limited to 800 MB due to some strict size limitations in the underlying file format. To ensure optimum performance for later data review Agilent strongly recommends not to exceed this database size limit. If a larger single database is required, Agilent recommends that the client/server version of the product be purchased. The client/server database uses Oracle, which allows for a much larger database. Additional standalone databases can be created via the Agilent ChemStore C/S utility.

Number of peaks	Agilent ChemStation report style	Run length (minutes)	Approximate size per run (KB)
4	short	6	10
4	short	30	40
4	extended performance	6	80
20	short	6	190
20	extended performance	6	300

Table 1
Client storage requirements for result only data storage

2. Agilent ChemStore C/S server Oracle® database system

Client hardware requirements

The following list shows the minimum requirements for the ***client*** in a client/server installation.

- 600-MHz Pentium III (Pentium IV recommend)
- 4 GByte of free hard disk space
- 128 MB RAM for single ChemStation instrument. 256 MB is recommended for best performance, for Windows XP the minimum requirement is 128 MB.
- 256 MB RAM for two ChemStation instruments (512 MB or more is recommended for best performance)
- Display: 1024 × 768; small fonts; 65-thousand colors

Client software requirements

- Windows 2000 Professional with Service Pack 4 or Windows XP Profession Service Pack 1a
- Microsoft TCP/IP protocol
- Microsoft Internet Explorer 5.5 or later
- Microsoft data access components (MDAC) 2.8 will be installed on your system. If you already use a later version of MDAC, or require for compatibility reasons a previous version, please contact your Agilent support representative for compatibility information.
- Oracle 9i client version 9.2.0.3.0. (included with the ChemStore C/S server software)
- Agilent ChemStation version A.10.01 or higher (optional)
- A local or network printer must be installed and configured.

Server hardware requirements

Agilent has optimized the performance of a ChemStation Plus client/server system to an average of 30 "concurrent" Agilent ChemStation/Agilent ChemStore Review clients, where concurrent clients are defined as clients connected to the central ChemStore C/S data organization system, that actively either spool data to the database or perform interactive queries (review client). Due to the nature of the application the impact of data retrieval is higher as this requires direct access to the database, while during acquisition the spooler is able to buffer data, thus ensuring a secure transfer in case of a network failure, for example. So the optimum number of concurrent clients might vary depending on the work practice in the laboratory. Depending on the combination of 2D/3D instruments, a typical high-end configuration can thus grow to approximately 30 acquisition clients with a maximum of 90 instruments. It is therefore recommended to use a high speed dual processor system with sufficient RAM.

The minimum requirements for the ***server*** in a Client/Server installation are the following:

- 600-MHz Pentium III processor
- 512 MB RAM
- RAID SCSI controller
- 6 disk drives - 9 GB or larger– 2 drives configured as a mirror set and 4 drives configured as a RAID-5 array
- Tape Device
- Uninterruptable Powersupply (UPS)

Note:
The drive configuration yields one mirrored partition for the operating system and application software, and one large array for the database files.

Server hardware considerations

The hardware requirements of the Agilent ChemStore C/S server will

	Entry level	Standard level	Highend level
No. of concurrent review clients	1-5	1-15	> 15
Processor speed (GHz)	1	1	1
Number of processors	1	1	2
RAM (MB)	512	1024	2048
Number of RAID controllers	1	2	2
Disks for operating system	2 × 18 GB RAID 1	2 × 18 GB RAID 1 (Controller 1)	2 × 18 GB RAID 1 (Controller 1)
Disks for Oracle database	3 × 18 GB RAID 5 RAID 5	5 × 18 GB RAID 5 (Controller 2)	5 × 36 GB RAID 5, (Oracle Data, Contoller 2) 2 × 18 GB RAID 1 (Index Log Files, Rollback Segments, Controller 1)
Hot swappable drives	yes	yes	yes
Backup device	DAT/DLT tape drive	DAT/DLT tape drive	DAT/DLT tape drive
UPS	yes	yes	yes

Table 2
Recommended server configurations for Agilent ChemStore C/S

vary based on the size of the database selected at installation time and the number of concurrent connections (the number of active instruments acquiring samples to the database and Agilent ChemStore C/S review clients) and the backup requirements for the server database. Table 2 shows three recommended server configurations. In a very small networked installation with less than three clients and no need for advanced security using RAID, the Chemstore C/S Oracle database can also run on a high-end PC using Microsoft Windows 2000 server software as operating system.

Note:
Planning the server disk configuration is very important:
12 GByte (for small database) to 54 GByte (for large database) hard disk, RAID 5 configuration is recommended. Using a RAID 5 hard disk configuration (redundancy and striping) yields less free hard disk space than RAID 0 (no redundancy). For example, 3 disks of 9 GByte each using RAID 5 yields 18 GBytes while using RAID 0 yields 27 GByte. RAID 5 is recommended for maximum performance and protection of your data. For backup operation of the database, the required disk space must be duplicated, that is a 54 GByte RAID 5 configuration should have an additional 54 GByte of disk space available for database backup. When calculating server memory requirements, calculate 8 MB of additional memory for each Agilent ChemStore C/S client. For more details on setup and configuration of the server, please refer to the *Agilent ChemStore C/S Installation* manual.

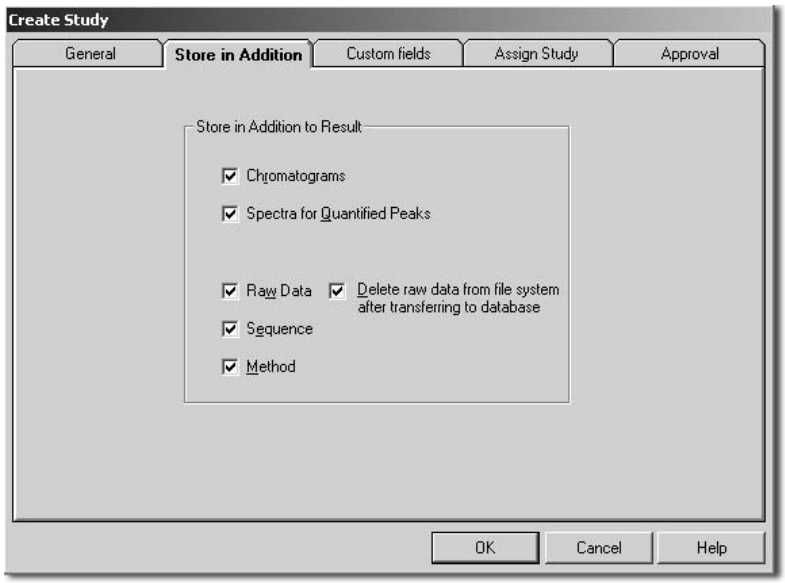


Figure 1
Study setup for full data integrity in the server database

Server software requirements

- Windows 2000 Server with Service Pack 4
- Microsoft TCP/IP network protocol
- Microsoft Internet Explorer 5.5 or later (for admin client only)
- Internet Information Server version 3 or greater (IIS is integrated into Windows 2000 Server
- Oracle 9i Standard Edition version 9.2.0.3.0 (included with ChemStore C/S server software)

Database size

The database size is selected at installation time and should be given careful consideration as this will affect the total number of runs which can be accessed online and the frequency of archive/dearchive operations. Archive with delete (to recover run space in the database) or dearchive operations (to access run data online). At installation time you can either select from the preconfigured databases configurations listed in table 3, or have a customized configuration.

Database configuration	Approx. no. of runs	Database size
small	≤ 7500	4 GByte
medium	≤ 25000	10 GByte
large	> 25000	40 GByte

Table 3
Database configurations

Note: The custom database configuration must be planned as a project with Agilent database consulting specialists prior to system installation. The size of the Agilent ChemStore C/S database is based on an Agilent ChemStore C/S system which has an average distribution of all Agilent ChemStation 2D and 3D techniques. Also, all *Store in Addition* checkboxes are enabled for all studies, as shown in figure 1. The space requirements for runs stored in the Agilent ChemStore C/S database will vary depending on your environment. A run is defined as a single set of results produced from a single sample acquisition or reprocessed by an Agilent ChemStation which has been transferred and stored in the Agilent ChemStore C/S database.

The actual amount of space consumed by each run in an Agilent ChemStore C/S database will vary depending on:

- the *Store in Addition to Result* settings of the study to which the run is assigned (table 4), and
- the technique and complexity (numbers of peaks, Agilent ChemStation reports, custom fields, and so on) of your chromatography for that run.
- For details on the size of raw data files by technique, please refer to table 5.

Supported Agilent ChemStation software

Agilent ChemStore C/S can be used with the following Agilent ChemStation software:

- Agilent ChemStation for gas chromatography, revision A.10.01 or later,
- Retention time locking software, add-on module for Agilent ChemStation for gas chromatography,
- Agilent ChemStation for liquid chromatography, revision A.10.01 or later,
- Gel permeation chromatography software add-on module for the Agilent ChemStation for LC,
- Agilent ChemStation for capillary electrophoresis, revision A.10.01 or later,
- Agilent ChemStation for liquid chromatography mass selective detection, revision A.10.01 or later.
- Agilent ChemStation for analog signal acquisition, revision A.10.01 or later,
- Agilent ChemStation for capillary electrophoresis mass selective detection, revision A.10.01 or later,
- Agilent ChemAccess C/S remote instrument control revision A.02.01, and
- Agilent ChemStation Plus Method Validation Pack A.02.01.

Store in Addition	Description
Chromatograms	Stores all available chromatograms (from each detector and/or signal)
Spectra for quantified peaks	Stores spectra from all peaks that have been identified and quanti fied as compounds in the calibration table.
Raw data	Stores the acquired data in addition to the calculated result. *Note:* This setting has a significant effect on the amount of storage space required for each run in the ChemStore C/S database. For example ChemStation data which is created from 3D techniques such as a liquid chromatography diode array detector will require more storage space than a 2D technique such as gas chromatography.
Sequence	Stores the ChemStation sequence.
Method	Stores the ChemStation method

Table 4
***Store in Addition* study settings**

Technique	Average file size (kB)
2D GC/LC	50
3D LC	60
3D LC/MS	750
3D CE	600

Table 5
Average raw data file size by technique

1. Data transfer

The Agilent ChemStation Plus concept consists of different software components designed for the various tasks in the chromatographic laboratory. The Agilent ChemStation manages data acquisition and data analysis, and the Agilent ChemStore C/S database offers advanced data and result management along with additional sample information management such as data organization, advanced result calculations, result approval, and archiving. This concept allows a clear separation of result rework and advanced result review and offers unmatched data integrity and traceability by tracking the data history — Results in ChemStore can only be under review or after review completion, locked and pending for archival, while results in ChemStation are under rework. It is therefore very important to have a secure and documented data transfer between the software application. The specifications will offer a detailed outline of the data transfer including security measures for both directions. To further manifest this separation between rework and review, results can be locked from further modification when giving an approval.

From Agilent ChemStation to ChemStore database

Agilent ChemStore C/S offers two modes of data transfer from the Agilent ChemStation into the Agilent ChemStore C/S database –

- interactive mode and
- automated mode.

Figure 2 shows the interactive mode.

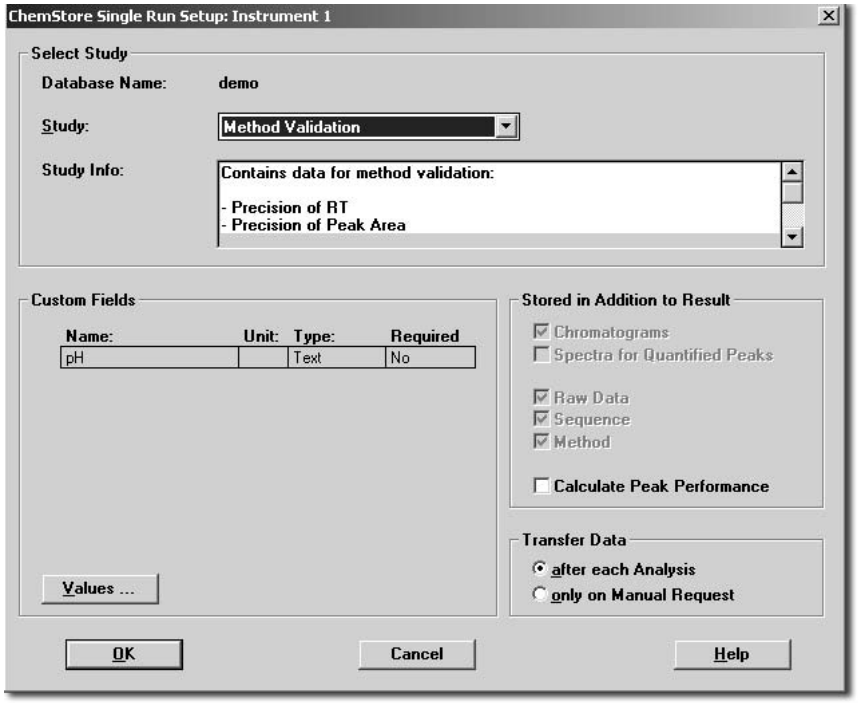


Figure 2
Data transfer setup screen in the Agilent ChemStation

Interactive mode
Users perform the transfer manually from the Agilent ChemStation menu item in "Data Analysis View" or use the batch review interface of the Agilent ChemStation. This mode of operation is useful for analysts who wish to perform a first pass data review from the Agilent ChemStation data analysis view before transferring the approved results to the database.

Automated mode
Results are transferred automatically to the database at the end of each run. This mode ensures that all analytical data are transferred into the Agilent ChemStore C/S server database and are protected from unauthorized modification. If the same sample injection is reanalyzed and then transferred, a new version of the result data is created, together with an entry in the audit trail of the Agilent ChemStore C/S database, thus ensuring a full history of the injection.

File security during data transfer
Each file that is transferred over the network from the ChemStation to the ChemStore database or back is protected with a hash value. The application software automatically calculates the hash value prior to any data transfer using a 24 character value based on the RSA Data Security, Inc, MD 5™ message digest algorithm. The hash value is stored with the data file. Whenever this data file is transferred over the network, e.g. for a reanalysis cycle, the same message algorithm calculates the hash value of

the current file and compares it with the stored value. Any difference is reported as an error and the data transfer is interrupted.

Assignment of studies and custom field information
Runs are stored in studies which form the top level hierarchical element of the Agilent ChemStore C/S database similar to a drawer in a cabinet. Study access is restricted to users that were explicitly granted the permission to access the data inside this study. Users must be assigned to a study in order to review study data or spool data into the study. The amount of result and meta data that is stored in the Agilent ChemStore C/S database is defined on a per study basis. For example, the transfer of a set of results may also include chromatograms and spectra, and the raw data, methods and sequence file used to produce those results.

Custom fields allow additional information or result fields to be linked to each set of results ("run"). They are used to store additional information that is not accessible from the Agilent ChemStation method or results, that is, information which may reflect other measurements (for example, LIMS ID, sample pH, patient weight, dosage, and so on) or may be used to organize the data (for example, the identification code of the test patient from whom a serum sample was obtained). These custom fields may be configured as "required" or "optional". For the former, a value must be specified before results can be transferred to the database or a sequence can be executed. Custom fields can also be used in later queries for reports, custom calculations or charts.

Study and custom field configuration
A custom field and its type are defined globally per database as shown in figure 3. The available field types are:
- True/False selection
- Configurable selection list
- Integer value
- Real value
- Text field
- Date or Date/Time

Custom fields need to be assigned to a study to activate them for use. As part of the study setup the user defines how the custom field is populated and whether it is a mandatory field or not. A custom field can be filled by a ChemStation function or manually. Manual fields can be flagged as "required" or a default value as well upper and lower limits can be specified.

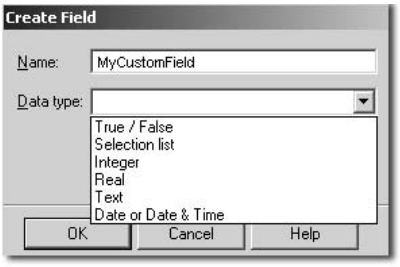


Figure 3
Creating a custom field

Custom field values are entered before the single sample or sequence acquisition:
- Single sample/manual operation: Study and custom field values are entered by a "single run" Agilent ChemStation menu item (figure 4).
- Sequence operation: Study and custom field values are specified per sequence line and and stored with the sequence.

Using Agilent ChemStore C/S data review capabilities, the lab manager or a quality control person can review data generated on multiple instruments throughout the lab. Samples can be approved, rejected, excluded or assigned for rework by the Agilent Chem-Station (see below *From database to the Agilent ChemStation*).

ChemStore spooler – Managing data transfer from Agilent ChemStation to Agilent ChemStore C/S
To ensure optimum performance of the Agilent ChemStation, a background spooler takes care of a secure result transfer from the Agilent ChemStation data into the Agilent ChemStore C/S database.

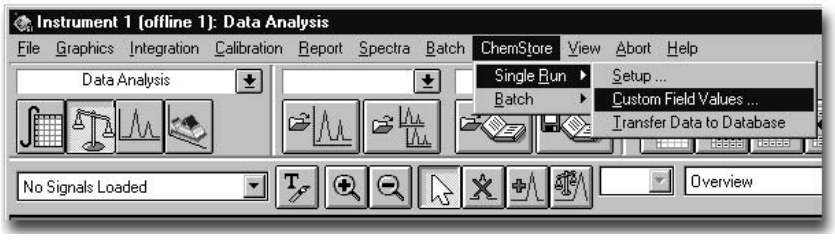


Figure 4
Data transfer setup screen in the Agilent ChemStation

This approach has several advantages, including

- releasing the Agilent ChemStation to go on with other tasks quickly while the transfer continues in the background and
- guarding against data loss in case the database insert operation fails or the network is down.

From database to the Agilent ChemStation

Runs which require further rework, for example manual integration, can be transferred from the database to the Agilent ChemStation. Agilent ChemStore C/S creates an Agilent ChemStation batch to ensure a consistent ease of operation. The setup for this batch submission is a two-step approach:

1. Create the batch request from the Agilent ChemStore C/S review client by marking the runs for transfer in the user interface. An authorized user configures the transfer details in an interactive pop-up window (figure 5). These include
   - assigning the run data to one or, in case of several runs, to more than one user for reanalysis on a per run basis,
   - optionally transferring the method with the data (including the choice between all versions of the method), and
   - entering a comment with each run transfer that will be displayed to the Agilent ChemStation operator.

2. Use the Agilent ChemStation *Load Batch from ChemStore* menu item to select the desired batch from the pool of pending Agilent ChemStore C/S batches to download the runs to the Agilent ChemStation. The operator then reviews the data in the ChemStation batch review and makes the necessary changes. After completion of the review the modifications can be transferred to the database as new result versions.

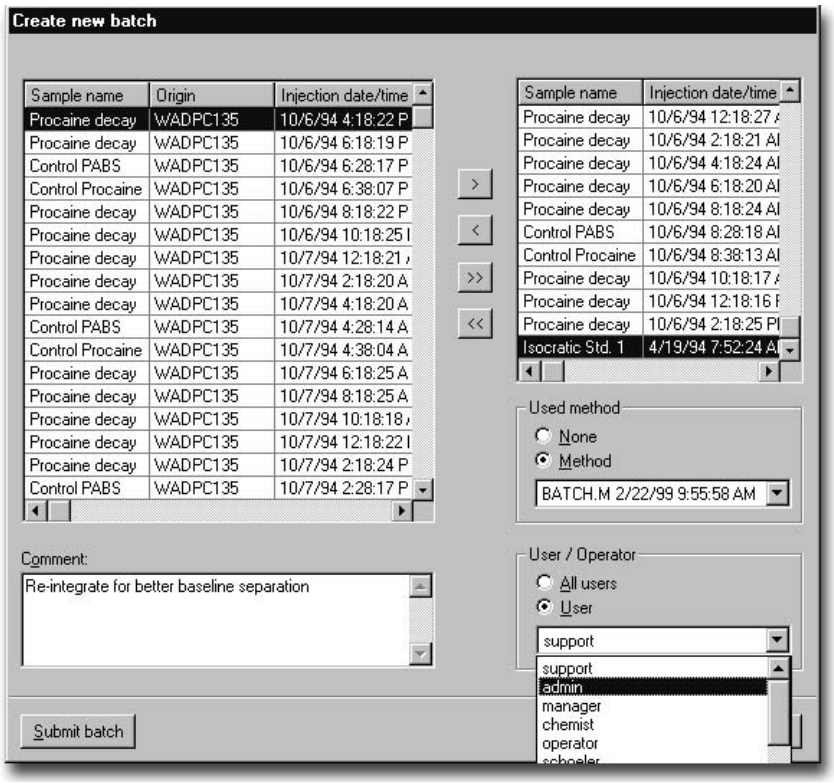


Figure 5
Batch setup for data transfer from database to the Agilent ChemStation

2. Task flow in the review client

Retrieve and review sample data

The ChemStore C/S review client provides two user interfaces for data review - the sample-centric *Sample* view and the compound-centric *Compound* view. Both views are further subdivided into a tabular display, with or without chromatograms and/or spectra, and a chart display for plotting sample- or compound-related data.

The task flow of Agilent ChemStore C/S is designed to support the laboratory's workflow and can be outlined as follows:

1. Select the database that contains the data you want to work with.
2. Extract the set of results you will work with. This is done via a database query and the results become the "current set

of data".

3. Perform any of the following tasks, in any order:

- Review the results "by sample" or "by compound". While reviewing the results, you may switch between any of several different data presentations (for example, a table, a chart, or plots of the chromatograms and or spectra). In addition, you may specify additional statistical computations to be done on the results and included in the tabular or graphical presentations.
- Generate a report on the data in the set of data. Any of a set of report templates may be used, and you may customize those templates according to your needs or create new ones.
- Export selected data. Data may be sent to an Excel 5.0 "*.xls" file or to an application that supports cut-and-paste of the appropriate format.
- Execute custom calculations such as cross-run or cross-compound calculations or advanced statistical calculations. Predefined templates can be modified or new ones can be created. Modifications are stored as new template version. Calculation tables and charts of calculated values can be integrated into the report.
- Set up a "batch" by marking runs whose data and method are to be transferred back to the Agilent ChemStation for reanalysis.
- Filter or exclude any run in the current data set.
- Approve or reject runs based on your result review. Both steps follow the FDA requirements for electronic signatures.

The standard query builder of ChemStore C/S provides fast access to the commonly used database fields for fast and easy data retrieval. For more sophisticated queries the advanced query builder provides for access to all database fields, conditional query capabilities as well as the use of variables for the operator name ("currently logged on user") and the date (for example "not older than 2 days").

Performing statistics calculations

The user may optionally select to have statistical calculations performed on the (numerical) data which is being reviewed, as shown in figure 6. This can be achieved using summary statistics that calculates statistical values based on a single column of numerical values. The calculated values are:

- number
- minimum
- maximum
- sum
- mean
- variance
- standard deviation
- relative standard deviation

In addition, *Regression Statistics* can also be used to calculate curves and statistics of two numerical columns. Curve types include:

- linear
- quadratic
- cubic
- logarithmic
- exponential
- power

The curve parameters for the curves and the residuals will be calculated and displayed. Residual and curves can also be displayed in a chart.

Custom expressions

Simple Mathematical calculations may be performed on results using the built-in expression definition interface (figure 7).

This offers the basic expression functions (addition, subtraction, division and multiplication) plus the following functions:

- exponential
- natural logarithm
- logarithm
- square
- square root

	Biphenyl			
Statistics	Amount	RT	Area	Height
Count	15	15	15	15
Sum	0.14	38.57	4074.03	559.70
Minimum	0.00536	2.56547	142.49	25.44
Maximum	0.01701	2.58024	452.50	58.34
Mean	0.00955	2.57133	271.60	37.31
Standard Deviation	0.0045	0.0051	127.4384	13.9228
Rel. Std. Dev. (%)	47.2374	0.1968	46.9210	37.3131
Variance	0.0000	0.0000	16240.5492	193.8437

Figure 6
Summary statistics

Custom calculations

The ChemStore C/S custom calculator provides all means to develop custom calculations that cannot be done with the simple expression builder. The custom calculator user interface for development of calculation templates is shown in figure 8. Calculation templates are fully versioned. The modification of an existing calculation template is stored as a new template version. Only users with the appropriate permission have access to the custom calculator.

For a fast and easy template development the custom calculator is equipped with eight wizards:

- *Create Table* defines the data items for the calculation
- *Create Subtable* defines a sub-set of data
- *Insert Column* allows to define columns that are populated with calculation results and can be used in further calculations
- *Define Variable* allows to specify variables (fixed values or calculation results) that can be used in further calculations
- *IF condition* defines conditional values, for example for limit checking, resulting in a configurable result output, such as “pass” or “fail”.
- *Format* defines the number format and precision of data items for reporting
- *Transpose* allows to transpose a table or subtable

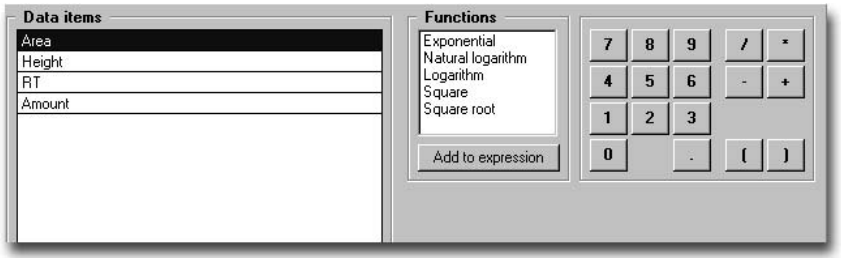
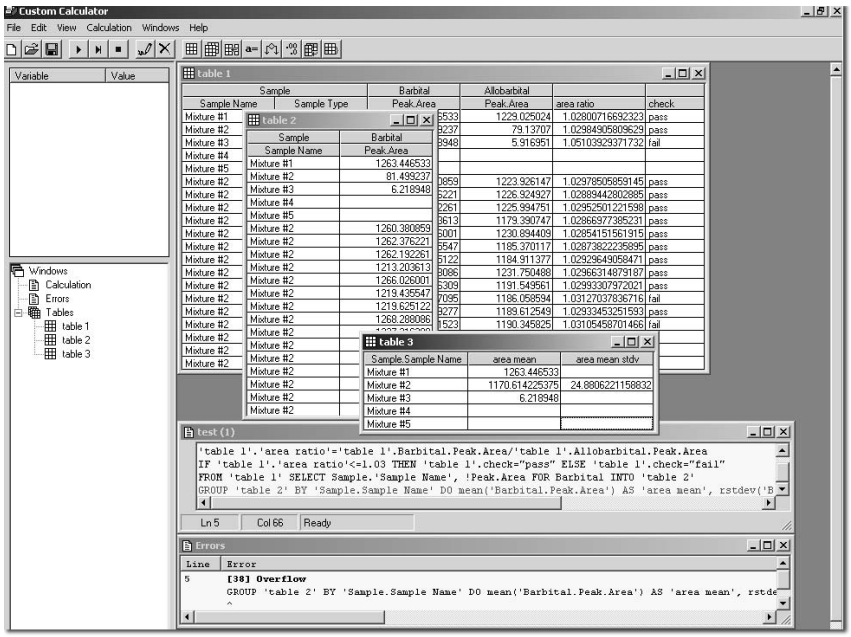


Figure 7
Setup of custom expressions



- *Group* allows to group by a specific data item and do statistical group calculations, such as
  – number of values (“count”),
  – maximum value,
  – mean value,
  – minimum value,
  – relative standard deviation,
  – standard deviation,
  – sum, and
  – variance.

The expression wizard (figure 9) is used for defining a calculation, which can be either an expression or condition. Calculations can be defined for all available columns or variables. It provides a set of arithmetical and statistical functions that can be used in conditions or expressions, these include:

- addition
- subtraction
- multiplication
- division
- absolute value
- count
- exponential
- logarithm
- natural logarithm
- mean value
- minimum
- maximum
- relative standard deviation
- square
- square root
- standard deviation
- sum
- variance

Multiple calculations can be defined within a single template based on any table or subtable.

All calculations are strictly column-based operations and easily allow any kind of cross-compound calculation, for example for the determination of relative retention times as required in some regulatory methods for confirmation of a successful identification or for calculating relative responses. The transpose wizard converts a table for doing cross-run calculations such as the comparison of results to a reference run. The group wizard provides for the ability of grouping a set of results by criteria

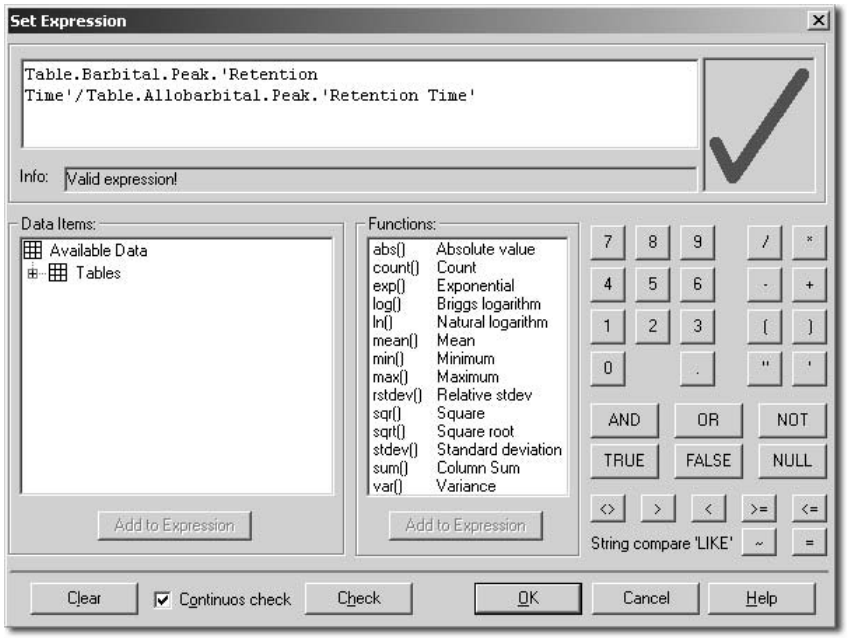


Figure 9
The expression builder of the custom calculator

stored in any other database field including custom fields. Groups of data can be used in statistical calculations, where the results may serve as a data source for further calculations. The IF condition wizard integrates with the expression builder and can filter result data based on virtually any condition. The output can be reported according to the specific laboratory or regulatory requirements, for example for limit checking – a sample result lying outside of a specified interval can be flagged as "out of spec.".

During the development the custom calculation is documented in a scripting window as shown in figure 8. This protocol is stored in the database as the calculation template. Each new version of a template is stored with version information. Optionally it can be included in the report to fully document the calculation.

Any part of the calculation or the complete template can be tested on sample data obtained by a database query. Any error or inconsistency is identified and documented in the error window. The related calculation piece is highlighted in the protocol for convenient and simple troubleshooting.

Calculation result tables as well as charted calculation results can be integrated into ChemStore reports. The user may choose whether to base a report on the latest version of a calculation or any earlier one. The reporting capabilities of ChemStore C/S are outlined in the following section.

Agilent ChemStore C/S — Reporting

Agilent ChemStore C/S offers a powerful report generator enabling users to easily create and generate final summary reports. The preview function helps to interactively develop the desired report without requiring test printouts. Agilent ChemStore C/S comes with a set of built-in templates to cover the most common needs for summary reporting. These templates can be used as a starting point to build your own customized reports.

Following is a list of built-in reports

- *Analysis Results* reports.
- *Audit Trails* reports
- *Compound Amounts* reports for individual results.
- *Instrument and Run* reports
- *Peak Details* reports
- *Kinetic Decay* reports.
- *Sample Summary* reports with numeric tables of the result information.
- *Sequence summary* report—a complete report for GMP requirements including summary statistics, graphics of chromatograms and spectra and result charts with control limits for each compound type grouped by the sample type.
- *System Suitability* summary reports including statistics over replicate injections.

The following are key customizable features of the reporting

- display of the selection criteria of the query,
- display of all custom calculations that have been used in the data section of the report
- an overall report header displayed on each page that allows to include graphic items such as a company logo,
- table information,
- configurable table contents and table header.
- fonts and font attributes,
- individual sections with additional individual headers containing data tables, chromatogram and spectra (if available from a diode array detector) or data charts,
- individual page breaks,
- additional sorting criteria within one data section to group data logically, for example, around a vial number, a sample type or any other item that the user requires,
- restriction capabilities to focus on an adequate subset of the data, that is, one peak within a chromatogram, and
- statistical calculations selected interactively at any time during the data review from the ChemStore C/S user interface.
- inclusion of custom calculation result tables, charts of calculated values and full documentation of the custom calculations, including calculation formula and calculation errors.

The ChemStore C/S application offers an additional functionality to print the current view. This function gives access to an immediate printout of the actual screen including all graphics without any formatting or configuration tasks.

For system suitability reports the calculation of system suitability parameters can be triggered independently of the ChemStation method during sample or sequence setup by enabling the "Calculate Peak Performance" checkmark per run or sequence line (see figure 2).

Agilent ChemStore C/S — Data Export into Other Applications

Agilent ChemStore C/S allows an easy export of selected database information (selection by records and data fields) to third party applications (notably MS Excel). The user has control over which fields are included and in which order. This can be done based on queries or reports exporting data into the native file format. Agilent ChemStore C/S also offers clipboard cut-and-paste for both tabular and graphical data (figure 10). Report outputs can be in a file format allowing convenient publishing of reports, for example, HTML for internet and intranet publishing.

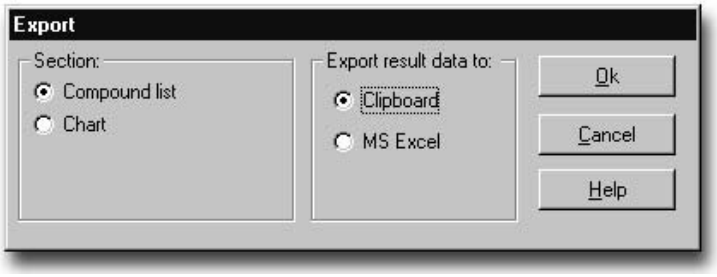


Figure 10
Interactive data export from Agilent ChemStore C/S into other applications

ChemStore C/S allows printing in the following file formats:

- HTML format for review with an Internet browser (excluding graphics).
- CSV format for spreadsheet applications
- XML format as generic file-interface (excluding graphics)

Agilent ChemStore C/S — User Interface

The Agilent ChemStore C/S review client offers the user two main "toolkits": data review and database administration. The latter will be described in the next section.

Sample and compound review

Within the data review toolkit, the user has a choice of whether to see data organized by analysis (also referred to as "run" or "sample") or by compound. In the table layout view data is displayed in configurable tables, either sample- or compound-centric.

Chromatogram/spectrum presentation

In the review layout view, the display area can contain both graphics and a table. The details differ for sample and compound review. The chromatogram viewer provides for dynamic zooming and rescaling capabilities, allowing a detailed inspection of the baseline to judge whether any rework of the integration is required.

General chart presentation

In the chart layout view the chart presentation is available only if no summary or regression statistics are in use. If regression statistics are being calculated, the regression chart and residual chart presentations replace it. Figure 11 is an example of a chart contained in the display area.

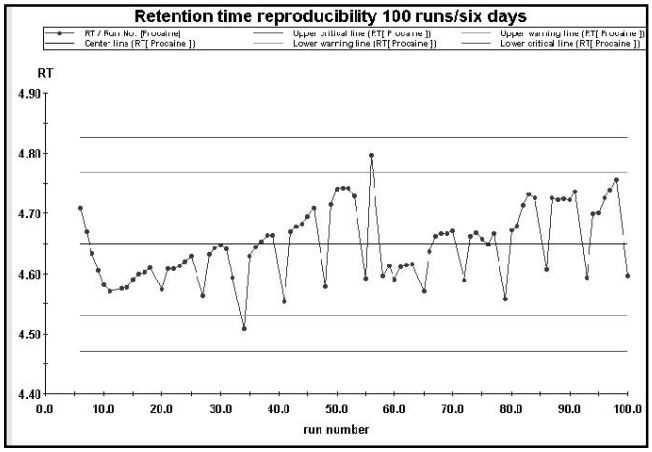


Figure 11
Chart for retention time reproducibility with warning and critical limits

Agilent ChemStore C/S — Security

Data acquisition, data analysis and data review are password-protected. Each user must have a valid user-id and a password to log on to the application, as shown in figure 12. To be able to transfer data to the database the user must be logged on to the database. User validation is done on a per database level and always requires to enter a user name and a password. Permissions for several tasks like approval or archival of runs, creation of custom fields, report templates, calculation templates or studies can be assigned to each individual user. Four user group templates for permission rights are supplied with the review client. They can be used as a starting point for the assignment of the permissions. Note that users and their security permissions are configured separately for each Agilent ChemStore C/S database. Users and their permissions can be imported from an existing database during creation of a new standalone database. In a client/server environment users are centrally managed in the Oracle database.

Electronic signatures and password security

Agilent ChemStore C/S uses electronic signatures based on the application User-ID/password combination to uniquely identify the users and their signatures. In order to keep the password unique to the individual user an additional security function is implemented to periodically check and revise passwords, and apply the company's password policy. *Minimum length* is the minimum acceptable length (in characters) of a password. *Password validity* is the length of time (in days) over which the password remains valid. *Minimum password recycle* is the minimum number of new, unique passwords that a user must use before a password can be used again.

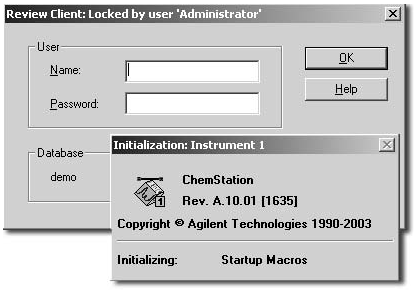


Figure 12
Password protection of the application software

Agilent ChemStore C/S — Database Administration, Backup and Recovery

Database administration

The review client provides the graphical user interface (GUI) through which the user can accomplish the following administrative tasks. Although the capabilities of the entry-level and client/server versions are to some extent different, the GUI is identical.

- Create a new database–(entry level database only),
- Compact (defragment) a data base–(entry level database only),
- Create or modify a study or custom fields,
- Administer system settings,
- Administer users and security,
- Manual or automatic archive, delete and de-archive data (server-only),
- Assign studies to users,
- Email notification for example on security violations (server-only).

The client/server version offers supplementary tools for administrators in the *Admin Client* to perform proper maintenance of the server database, archive/dearchive or archive/delete functions and other setup tasks. The Agilent ChemStore C/S *Admin Client* is a web-based application that can be run from any PC on the network. The *Admin Client* performs the following main tasks on the server database using a service running on the server.

- Schedule archive, dearchive and delete operations.
- Modify scheduled operations.
- View reports detailing pending operations.
- Review archive and dearchive history.
- View information about archives, runs and other objects, including a list of all runs in the archive unit.
- Execute archive, dearchive and delete operations immediately.
- Keep an audit trail of all archive and archive delete operations.
- Add and modify database connections to offer connection to a second Oracle database.

Database backup and recovery

One of the most important IT routines is the implementation of a Backup and Restore concept. Backups and – equally as important – the ability to restore a backup are important tasks in order to protect business data and laboratory investments.

Agilent Technologies can provide assistance in creating, implementing and testing a ChemStore C/S Server Backup and Restore strategy. This strategy should ideally be planned before the implementation but Agilent offers both, a service prior to the installation as well as a post implementation service.

For this purpose a ChemStore C/S Backup & Recovery strategy paper has been developed. With this strategy paper and by working with a customer's ChemStore C/S administrator Agilent provides a consulting service to plan and implement the right backup and recovery strategy for your business.

With a working knowledge of implementing solutions Agilent uses software from Veritas called Veritas Backup Exec™ for Windows 2000, Backup Exec Agent for Oracle™ and Backup Exec Intelligent Disaster Recovery.

Agilent ChemStore C/S — Archiving Data

The client-server version provides for manual or automatic archiving of runs present in the database to a separate file on disk or tape.

Manual archiving

Manual archiving is done from the "Archive/Delete" view in the ChemStore C/S review client and is based on the selected data set. Manual archiving requires the user to have the permission for archival. Individual runs or the whole set of runs are marked interactively for archival. These runs are then scheduled for the next archival operation on the server.

Automatic archival

An administrator with archival permission can set up a list of individual archive queries for automatic archiving, which are executed at predefined time intervals. Each custom query is put together from a set of criteria, including for example, injection time, sample name, instrument name, operator name, sequence name, method name, study name, custom field values, approval status and so on (figure 13). The available operands depend on the data category (text, numeric values, date) including wildcards and relative values (for example, runs "older than x days"). For performance reasons the number of clauses that can be defined for automated archival is restricted to 10.

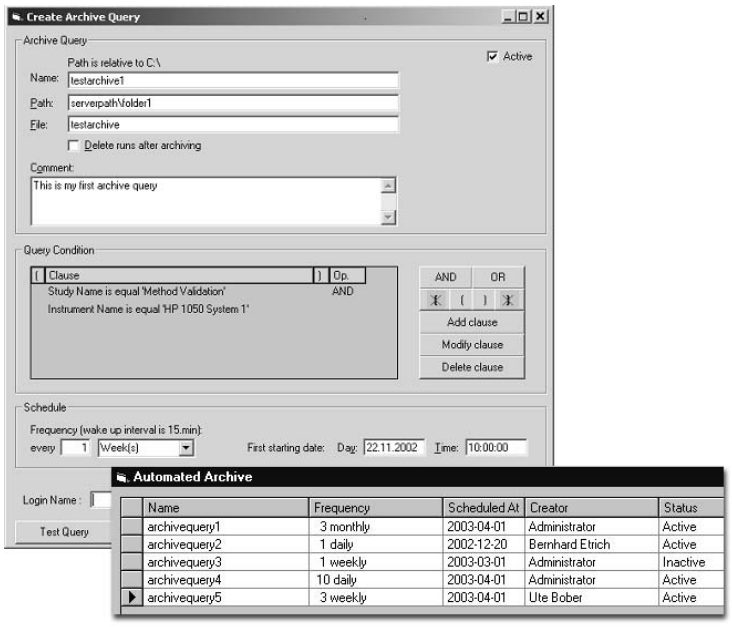


Figure 13
Setup of automatic archive queries

Each archive query is stored under a unique user-defined name and can be executed based on a configurable time interval (per query), for example, daily, weekly, monthly or in conjunction with a counter such as every x days. A test functions allows the user to obtain information on the number of runs that the query returns at the moment with the given query condition. For each archive query the name and path for the archive unit have to be specified. The filename for the automatic archive file is appended with the archival date, resulting in a file name format "<filename>-yyyy-mm-dd". Each archive query can be disabled when not required permanently. After successful completion of the archive the data can be automatically deleted to create free space in the database.
Both manual and automatic archival require re-identification with user-ID and password.

A checksum-protected archive catalog file in XML format is generated with each archive unit, which contains detailed information about the content of the binary archive file. A generic archive interface provides a closer linkage to other applications for enhanced archive management (for example, archive management or hierarchical storage management systems).

Agilent ChemStore C/S — LIMS Connectivity

ChemStation Plus can be easily connected to a Laboratory Information Management System (LIMS). For this purpose the Agilent ChemStation provides for a sample list import function to conveniently translate a work list from the LIMS into a ChemStation sequence. An instant, file-less result transfer back to the LIMS from the ChemStore C/S database (server only) is achieved through the integrated ChemStore C/S LIMS interface.

Sample list import from LIMS

The sample list generated by the LIMS can be imported to the Agilent ChemStation as a ChemStation sequence in XML-file format. XML is a very portable and flexible protocol for interconnectivity between systems.

The sample list must contain a LIMS ID for each sample. This LIMS ID is mandatory for sample tracking from and result transfer to the LIMS. Optionally additional two fields can be populated with LIMS-specific data.

Result update to LIMS

ChemStore C/S provides for file-less access to all result data stored in the database as LIMS data (identified by the LIMS ID). This is achieved through a combination of read-access to all result data in the database as well as a controlled write-access for the LIMS. Prerequisite for results to be accessible by LIMS is the existence of a LIMS ID which is assigned per sequence line. In addition a LIMS notification may be used, which is tied to the approval of data as shown in figure 14. The administrator may decide which approval level is appropriate to initiate the LIMS transfer. In addition the LIMS can acknowledge data that was successfully transferred to LIMS to exclude it from future updates.

Workflow

The workflow can be divided into five sequential activities shown below:

1 The sample list is generated by the LIMS system in an XML format
2 It is imported by the Agilent ChemStation and translated into a ChemStation sequence
3 Samples are analyzed, results are calculated and stored in the ChemStore C/S relational Oracle database

4 Information typically required by LIMS systems are instantly made accessible in the ChemStore C/S database (tied to the existence of the LIMS ID)
5 If enabled on the system or for a specific study, a LIMS notification is triggered upon the approval of data (as configured in the approval configuration console)
6 A program from the LIMS systems can scan a table in the database for a specific update flag to see if any new records are available for processing, and can amend the flag so that it is not scanned during subsequent scans.

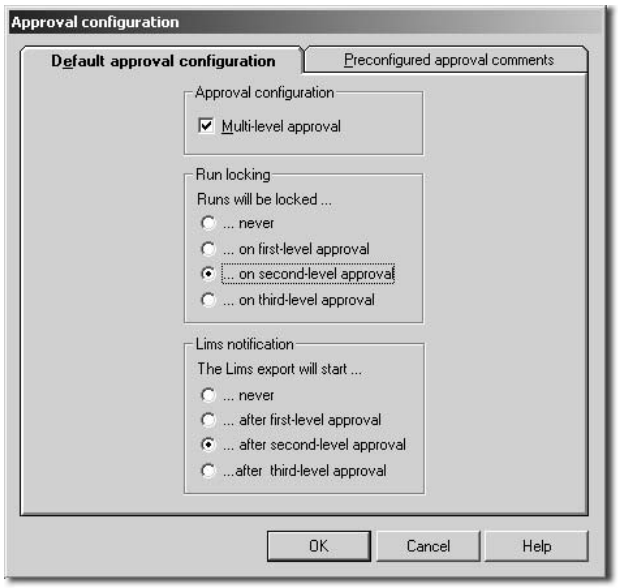


Figure 14
Configuration of approval levels and LIMS transfer

Agilent ChemStore C/S — Installation and Upgrading

The standalone version of Agilent ChemStore C/S is user-installable from the ChemStore C/S CD-ROM and can be added to an existing ChemStation installation (Agilent ChemStation software family CD-ROM version A.10.01 or higher).

The Agilent ChemStore C/S Oracle client/server version includes :

- ChemStore C/S server software (included on the ChemStation Plus CD-ROM),
- Oracle 9i standard edition version 9.2.0.3.0 (included in ChemStore C/S server software on a set of separate CD-ROMs),
- ChemStation Plus CD-ROM, and
- ChemStore C/S client software (on ChemStation Plus CD-ROM).

Agilent ChemStore C/S database migration

The Agilent ChemStore C/S system includes a migration utility which enables you to migrate your Agilent ChemStore C/S data in the following ways:

- Migrate Agilent ChemStore A.01.03 or B.0x.0x data (standalone) to Agilent ChemStore C/S B.03.01 (standalone).
- Migrate Agilent ChemStore C/S B.03.01 data to Agilent ChemStore C/S server data.

If you are currently running Agilent ChemStore A.01.03 on your system, and you wish to migrate your data to the Agilent ChemStore C/S server Oracle database, you will need to migrate in two steps. First migrate to the B.03.01 Agilent ChemStore C/S standalone database, then migrate from there to the Oracle database.

Standalone version

The complete Agilent ChemStore C/S standalone software is provided on the Agilent ChemStation Plus CD-ROM as described in table 6a.

Agilent ChemStore C/S server

The Agilent ChemStore C/S server product includes the ChemStation Plus CD-ROM and Oracle 9i revision 9.2.0.3.0 software on a separate CD-ROM offering one Oracle standard edition license. In addition an application-specific full user license is required and sold from Agilent for each additional user running a ChemStore review client. Five application-specific named user licenses are already included with the Agilent ChemStore C/S server software. Refer to table 6b for details.

Description	Product No.
Software module to add Agilent ChemStore C/S to an existing ChemStation for GC, LC, LC/MSD, CE, CE/MSD or A/D.	G2181BA
License to use the ChemStore C/S database module on another computer. Must either be on the same order as G2181BA or the customer must supply the license number for the original software. Does not require ChemStation.	G2186BA
ChemStation Plus client upgrade software, upgrades a single ChemStation Plus client to the latest software revision. Requires valid software licenses and ChemStation upgrade software G1656A.	G1657A

Table 6a
Agilent ChemStore C/S standalone version

Description	Product No.
ChemStore C/S client/server version. Includes ChemStore C/S server software Oracle standard editions, 5 Oracle application-specific named user licenses.	G1410A Qty: 1 per server
Oracle named user license for Agilent NDS Required for each additional named user of the ChemStore C/S server database.	G1411A Qty: (number of named users) –5
Software module to add Agilent ChemStore C/S to an existing ChemStation for GC, LC, LC/MSD, CE, CE/MSD or A/D.	G2181BA Qty: 1 per server
Licence to use the ChemStore C/S review client on another computer. Includes one online ChemStore license for use with an online data acquisition ChemStation plus an additional offline ChemStore license for offline data review	G2186BA Qty: (number of clients connected to the server) –1
ChemStation Plus client upgrade software, upgrades a single ChemStation Plus client to the latest software revision. Requires valid software licenses and ChemStation upgrade software G1656A.	G1657A
ChemStation Plus server upgrade software Upgrades ChemStation Plus server software to the latest revision. Includes G1656A ChemStation software upgrade. Requires valid software license.	G1655BA

Table 6b
Agilent ChemStore C/S client/server version

Agilent ChemAccess C/S

Product description

Agilent ChemAccess C/S is a client/server application which facilitates the secure and controlled integration of Agilent ChemStations into a networked environment by enabling users to:

- monitor and control instruments from any client on the network, for the following instrument modules:
  HP 1090 Series and 1050 Series, Agilent 1100 Series, Agilent CE system, Agilent 5890, 6850, 6890 GC systems, Agilent 5972, 5973A and 5973N GC/MSD system, Agilent 1100 LC/MSD system, Agilent 35900 A/D converter
- provides flexible centralized data organization features which allows Agilent ChemStation files to be automatically and securely stored onto the Agilent ChemAccess C/S server. This functionality is largely superceded when combining or adding Agilent ChemStore C/S to a Agilent ChemAccess C/S system.

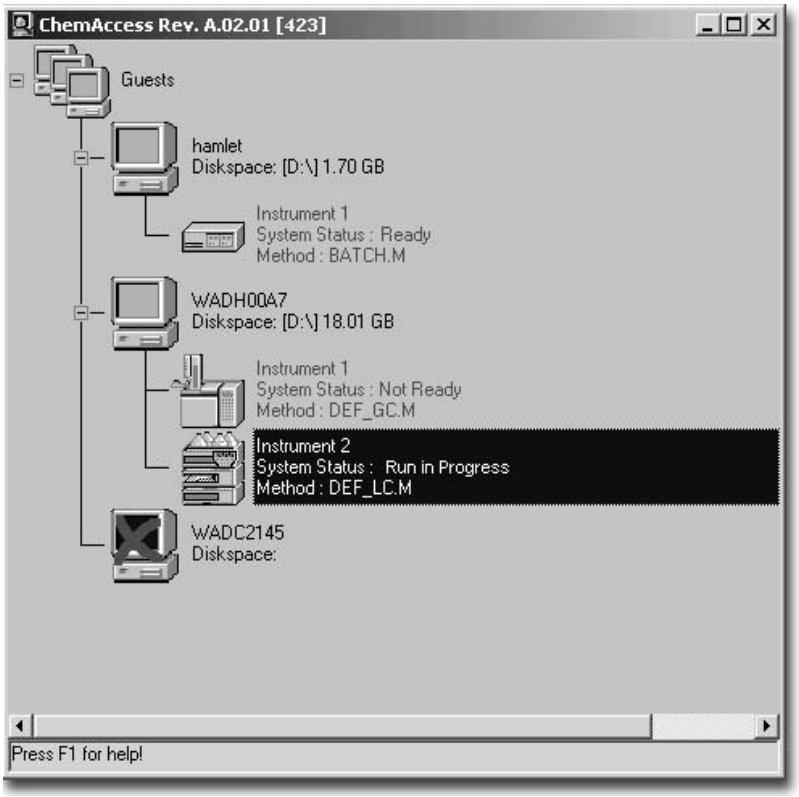


Figure 15
Agilent ChemAccess C/S remote status and control user interface

An Agilent ChemAccess C/S data system contains Agilent ChemStation clients, the Agilent ChemAccess C/S software and a Microsoft Windows NT server. Agilent ChemAccess C/S is compatible with both the multi-technique Agilent ChemStation and data analysis versions, enabling flexible and cost effective remote status monitoring control and review from locations which are situated away from the laboratories instrumentation.

Remote status and monitoring and control

From any Agilent ChemAccess C/S client an authorized user can remotely perform the following tasks on a remote instrument:

- Start and stop the method or sequence currently running.
- Assign a method or sequence
- Real time plot of the instrument signals.
- Execute a remote Agilent ChemStation command.
- Monitor the status of the remote PC's resources (disk space, memory and software revisions).
- Monitor the status of the Agilent ChemStation and instrument modules. Details are shown in figure 15.

Data storage and organization

Agilent ChemAccess C/S enables the Agilent ChemStation results (raw data, methods and sequences) to be securely stored on the Agilent ChemAccess Windows NT server. The results can be transferred automatically at the end of each run or interactively through the data analysis view of the Agilent ChemStation. If the same results are retransferred to the server, Agilent ChemAccess C/S employs data versioning to ensure that an entire record of the analysis is recorded.

Agilent ChemAccess C/S — System Requirements

Client hardware requirements

Agilent ChemStation and ChemAccess C/S

The PC client should conform to the requirements as specified in *Agilent ChemStation Specifications* (Agilent publication number 5988-9925EN). In addition to these requirements further 8 MB memory is required for network connectivity software and Agilent ChemAccess C/S software.

Agilent ChemStation, ChemAccess and ChemStore C/S

Configure the client using the Agilent ChemStore C/S client hardware requirements specified in this document.

Client software requirements

The ChemAccess C/S client module can be added to the Agilent ChemStation. The ChemAccess C/S module is supported with the following ChemStation software packages:

- Agilent ChemStation for gas chromatograhpy mass selective detection revision C.00.xx,
- Agilent ChemStation for gas chromatography, revision A.08.04. to A.10.0x,
- Retention time locking software, add-on module for Agilent ChemStation for gas chromatography,
- Agilent ChemStation for liquid chromatography, revision A.08.04. to A.10.0x,
- Gel permeation chromatography software add-on module for the Agilent ChemStation for LC
- Agilent ChemStation for capillary electrophoresis, revision A.08.04. or later,
- Agilent ChemStation for liquid chromatography mass selective detection, revision A.08.04. to A.10.0x,
- Agilent ChemStation for analog signal acquisition, revision A.08.04. to A.10.0x, and
- Agilent ChemStation for capillary electrophoresis mass selective detection, revision A.08.04. or later.

Each Agilent ChemStation that is integrated in an Agilent ChemAccess C/S system should conform to the following Agilent ChemStation and Windows software revisions:

- ChemStation for GC, LC, LC/MSD, CE and A/D revision A.08.04 to A.10.0x, on Windows NT 4.0 Service Pack 6a or Windows 2000 Service Pack 2-4
- GC/MSD ChemStation revision C.00.xx on Windows NT 4.0 Service Pack 6a.
- GC/MSD ChemStation revision D.00.xx on Windows NT 4.0 Service Pack 6a or Windows 2000 Service Pack 2.

Note:
Agilent ChemAccess C/S currently does not support the Agilent ChemStation for UV-visible systems.

Server hardware requirements

Agilent ChemAccess C/S supports up to 15 “concurrent” Agilent ChemAccess clients, where concurrent is defined as a client connected to the Agilent ChemAccess C/S server which either transfers result data from the Agilent ChemStation to the server for data storage or performs remote real time plot. Recommended server configurations are listed in table 7.

Note:
For a ChemStation Plus server system which has both Agilent ChemAccess and Agilent ChemStore modules, use the Agilent ChemStore C/S server requirements. Disk configurations may need to be customized to fit to your laboratories online and to long term storage needs.

Server software requirements

- Windows NT 4.0 with Service Pack 6a or Windows 2000 Service Pack 2
- Microsoft TCP/IP networking (supplied with Windows NT and Windows 2000).

	Entry level	Hi-end
Number of clients supported	1-10	1-15
Agilent NetServer model or equivalient	LC2000	LH3000
Processor speed (MHz)	933	1 GHz
Number of processors	1	1
RAM	384 MB	512 MB
Disk (number and size)	3 x 18 GB	2 x 18 GB, 3 × 18 GB
Raid level	five	one and five
Hot swappable drives	yes	yes
Network interface card	1	1

Table 7
Recommended server configurations for Agilent ChemAccess C/S

Agilent ChemAccess C/S — Product Options and Configurations

The complete Agilent ChemAccess C/S software is provided on the Agilent ChemStation Plus CD-ROM. This includes the software listed in table 8.

Description	Product No.
ChemAccess server software for remote status, monitoring and control of 16-bit ChemStation. Includes 10-user licenses for 3D data analysis software and a 2-user license for the GC/MS data analysis software	G1494A
ChemAccess client software, 5-user license remote status, monitoring and control client software for 16-bit ChemStation.	G1495A
ChemStation Plus server upgrade software. Upgrades ChemStation Plus server software to the latest revision. Includes G1656A 16-bit ChemStation software upgrade. Requires valid software license.	G1655BA

Table 8
Agilent ChemAccess C/S software

3. Agilent ChemStation Plus Security Pack

What's new?

Please refer to the section on new features in ChemStore C/S on page 2.

Product Description

The ChemStation Plus Security Pack is a module of the Agilent ChemStation Plus Series designed to support the requirements of 21 CFR Part 11. In the Agilent ChemStation the ChemStation Plus Security Pack modifies data analysis and provides advanced data management with regard to supporting the requirements for electronic records. It also offers a procedure to sign off runs with an electronic signature. To support the typical approval workflow in a regulated laboratory the Security Pack optionally provides for three levels of approval which can be combined with run locking. It offers an easy upgrade for an existing ChemStation installation.

The Agilent ChemStation Plus Security Pack is compatible with the following ChemStation modules:

- Agilent ChemStation for GC, LC, A/D, CE, CE/MS and LC/MS for instrument control and data analysis
- Agilent ChemAccess C/S remote instrument control
- Agilent ChemStore C/S data organization and data storage module
- Agilent ChemStation Plus Method Validation Pack

The UV-Vis as well as GC/MS ChemStation offer separate solutions for 21 CFR Part 11. Please refer to the specifications of the UV ChemStation Security Pack and the MSD Security ChemStation included in publication number 5980-0337E and 5989-0848EN, respectively. The ChemStation Plus Security Pack is available as a standalone solution or in a fully integrated client server network connected to the ChemStore C/S server Oracle database. It provides full support of 21 CFR Part 11 by offering advanced data security, data integrity and full change documentation in audit-trails. Specifications of the ChemStore C/S database module are available in the ChemStore C/S section of this document.

To achieve data security, the ChemStation Security Pack utilizes a combination of Windows user accounts and file permissions and auditing. In addition, it utilizes an application-related second layer of data security based on standard database security features. The application-related security requires a valid ChemStation Plus user account allowing the log-on to the application. A user with administrative priviledges can assign appropriate user permissions to other users within the ChemStation Plus software.

The ChemStation Plus Security Pack software allows to match user tasks in the laboratory with user roles in the software. It modifies the ChemStation operator rights, allowing to routinely operate the ChemStation application in the operator mode. For proper use and to achieve the best data security capabilities all users except those with administrative functions should utilize the ChemStation operator mode.

To achieve data integrity, all users are required to log on to a single database. This database (determination of the database connection requires the log-on to the Windows operating system with a Windows administrator account) will store all raw, meta and result data. In addition, any recalculation of results in the ChemStation will automatically be recognized as a new result version and will be transferred to the database as a new version. This versioning assures that no data is ever lost or overwritten and that a complete chain of events is documented. If a new result version is generated interactively, the user is forced to enter a mandatory comment, which is written to the audit trail.

To achieve data traceability, the ChemStation Plus Security Pack utilizes logbooks and audit trails that document who did what, when and why. These logbooks and audit trails are user-independent and cannot be modified or deleted.

All data is in electronic format and capable of long-term storage through archive/restore as well as viewing and printing in human readable format.

Key product features of the ChemStation Plus Security Pack include storage of all chromatographic data in a relational database, secured through

- password protection to access the data,
- full data protection using Windows security and database security features,
- application protection with a mandatory log-in, consisting of both identification components - user-id and password,

- user management with individual user profiles and privileges for the application – independent of the user privileges assigned for the operating system,
- an application-specific session lock allowing to explicity lock one ChemStation session while leaving a second instance running on the same PC, and
- a configurable time-based application lock to lock the current ChemStation or ChemStore session after a specified time of inactivity and thus avoids any unauthorized access to the application.
- A completely revised ChemStation operator access level which allows operating the entire application as ChemStation operator.
- A configurable access to the ChemStation commandline independent of the ChemStation user level, thus also preventing access for ChemStation managers.
- A modified batch review interface providing an automated user-independent data versioning with detailed audit-trails for all modifications.
- Complete change control documentation for methods and manual integration changes.
- Four levels of audit-trails for data acquisition, data analysis application tasks and security violations.
- Electronic signatures for each result version following the guidelines of 21 CFR Part 11.
- Three configurable levels of approval.
- Optionally locking of runs upon the approval to prevent them from further modification.

ChemStation Plus Security Pack — System Requirements

Client hardware requirements

The following list shows the minimum hardware requirements for this application:

- 600-MHz Pentium III (Pentium IV recommend)
- 4 GByte of free hard disk space
- 128 MB RAM for single ChemStation instrument. 256 MB is recommended for best performance, for Windows XP minimum requirement is 256 MB.
- 256 MB RAM for two ChemStation instruments (512 MB or more is recommended for best performance)
- Display: 1024 ∞ 768; small fonts; 65-thousand colors

Client software requirements

The following list shows the minimum software requirements for this application:

- Windows 2000 Professional with Service Pack 4 or Windows XP Profession Service Pack 1a
- Agilent ChemStation revision A.10.01 or later
- Microsoft Internet Explorer 5.5 or later
- Microsoft data access components (MDAC) 2.8 will be installed on your system. If you already use a later version of MDAC, or require for compatibility reasons a previous version, please contact your Agilent support representative for compatibility information.
- A local or network printer must be installed and configured.
- The hard disk partition that is used for installation of Security Pack must be formatted with NTFS.

The standalone database size is limited to 800 MB due to some strict size limitations in the underlying file format. To ensure optimum performance for later data review Agilent strongly recommends not to exceed this database size limit. A configurable size-checking tool automatically launches a warning message when the specified size limit is reached.

If a larger single database is required, Agilent recommends that the client/server version of the product be purchased. The client/server database uses Oracle, which allows for a much larger database. Table 9 gives some data on the time required for downloading data from the standalone database into the active memory of the client. The time mainly depends on the size of the standalone database, the number of runs marked for download and

the performance charactistics of the computer. All runs were stored with raw data, methods, sequences, and all result versions. The PC used for the test was below the recommended configuration (Kayak PIII, 450 MHz, 128 MB, and no data acquisition running in the background).

Database Size	No. of peaks	No. of runs	No. of runs loaded from database	Time [s]
93986	2137	240	100	17
192048	4642	410	100	17
445826	22621	868	100	13
			683	76
1048472	36710	2203	100	13
			683	59

Table 9
Run download time depending on the number of runs selected for download and the database size.

Working with ChemStation Plus Security Pack

Result management

The ChemStation Plus Security Pack is designed to store ChemStation data in a relational database by transferring it as a post-data analysis spooling job to the database. Depending on the laboratory workflow the data analysis can also be separated from the acquisition. In this case only raw and meta data are automatically spooled to the database, without a first set of data analysis results (data is acquired in acquisition-only mode). The ChemStore C/S ODBC spooler is a proprietary tool managing the transfer and protecting data against loss, modification or damage in case of transfer problems or network errors.

Data protection

Using the Security Pack in the standalone version, all data is stored in a single database file. The subdirectory storing the database files is protected with Windows file security permissions and only allows write access for members of the Windows user group.

The application denies access to data without a valid ChemStation Plus user-id and password. Any attempt to access the data in the standalone database directly with another application such as MS Access fails as it requires a password/user-id combination that is strictly confidential and only known by Agilent. It is not known by or given to any Agilent customer or user of this product.

In client-server installations of ChemStation Plus Security Pack direct, uncontrolled access to data in the Oracle database without using the ChemStore user interface is virtually impossible. This is because users must have a valid Oracle user account and they must have access to the data dictionary describing the meaning and contents of the Oracle tables and table columns. The dictionary is only available from Agilent Technologies against a written Confidentiality Agreement and should not be available for application users. Overall the attempt to falsify or delete data requires the collaboration of the user and the database administrator that provides the direct database access. Sufficient security constraints need to be imposed within the organisation to prevent any uncontrolled modifications.

Data storage

By default the the database stores the following data:

- calculation results of the ChemStation,
- contents of the ChemStation data directories; the *.d directories including the chromatographic raw data files,
- current method used for data acquisition and data analysis,
- current sequence, if a sequence was run to acquire or reprocess data,
- sequence, run and method logbooks,
- detector channel chromatograms as images according to the report configuration of the method, and
- apex spectra of all identified peaks in a chromatogram, when using a 3D detector.
- Optionally all peak performance parameters independent of the ChemStation method.

Protection of temporary data files

The ChemStation uses a given data directory structure to store acquisition and result data. The ChemStation Plus Security Pack also protects this data. After completion of data acquisition and a first result calculation, by default the data transfer is immediately initialized through the ChemStore spooler and the *.d directory with all its contents is deleted from the local hard disk (these default settings can only be modified by a user with administrative rights in the database). From then on, the data security mechanisms of the database itself secure the data. The temporary directory where the database spooler stores intermediate data is protected using Windows NTFS file and folder security.

If a first pass review in the ChemStore review client results in the need for some reanalysis work, for example reintegration, the data is submitted as a batch to ChemStation. This requires restoring data files to a temporary subdirectory. The Security Pack protects this subdirectory hpchem/x/data/chemstor where x is the instrument session number with read-only access for members of the Windows users group thus denying unauthorized access for operators.

Configuration and data protection using Windows security features

For security reasons, a user must be a member of the Windows user group *Administrators* or *Power Users* to access the configuration of the ChemStation Plus Security Pack. It restricts access to all data directories on the local PC with important information using the Windows users group privileges. The default configuration automatically sets all directory permissions and access limitations as part of the installation using the Windows groups “Users”, “Power Users” or “Administrators”. Each ChemStation user has to be member of either one of the groups.

Note:
Normal users must not be members of the Windows Administrators nor Power Users groups. The membership to these groups should be dedicated for system administrators.

Table 10 gives an overview of the permission rights that are limited to members of the Windows Adminstrators and Power Users groups.

User task	Granted to members of Windows User group	Granted to member of Power Users or Administrators group
Create a new MS Access database	no	yes
Configure database Alias	no	yes
Access the ChemStore ODBC spooler to resume interrupted data transfer	yes	yes
Access to the selection list of available databases	no	yes

Table 10
Tasks requiring membership in the Windows Administrators or Power Users group

Local directories storing relevant chromatographic data are also protected with Windows file and directory permissions. Table 11 gives an overview of the Windows permission rights on the data directories and files on the local hard disk. The first item in brackets displays the permission rights on the folder; the second item displays the individual file permission rights.

Note:
Windows file security does not give any access to a folder or directory for users that do not have access rights to the folder, even if the user has control over the files in the folder.

File path	Permission Windows Users	Permission Windows Administrators or Power Users	Directory/file owner	Data directory contents
\hpchem\chemstor \database	(W)(full)	(full)(RWXD),	All members of local Administrators or Power Users group	Contains database *.mdb file storing all raw and meta data
\hpchem\chemstor \spool	(WX)(full)	(full)(RWXD)	All members of local Administrators or Power Users group	Spooler jobs and data files
\hpchem\chemstor \hputil00.exe	none	(full)	All members of local Administrators or Power Users group	Access to ChemStore utility tool to create/ copy and manage local database files
\hpchem\X (instrument session number)\data\chemstor	(WX)(Full)	(full)(RWXD)	All members of local Administrators or Power Users group	Stores data files reloaded from ChemStore database to ChemStation batch review

Table 11
Directory and file permissions [(directory)(file)] set by the ChemStation Plus Security Pack [W=write, R=read, X=execute, D=delete, full=all permissions]

ChemStation Plus Security Pack — User Management and Application Security

User management and ChemStation Plus Security Pack user access rights

Security Pack provides a fully integrated user management that is independent of the Windows operating system. The user management covers both the ChemStation Plus data acquisition and data analysis tasks and the ChemStore C/S database data review privileges. The entire user administration itself is a user-privilege granted to administrators in the ChemStore C/S database. The ChemStation Plus Security Pack includes a modified ChemStation operator level allowing operators to perform all important acquisition and data analysis tasks for daily operations. Table 12 shows the most important changes in user privileges compared to the standard ChemStation for data acquisition. The ChemStation Manager always has access to all tasks within the ChemStation with the exception of access to the ChemStation command line. Unlike the standard ChemStation this privilege can be assigned individually and is not tied to any ChemStation user level (see figure 16). A detailed documentation of the data review user privileges in the ChemStore C/S database is in the ChemStore C/S concept guide.

User privilege	Security pack operator	ChemStation operator
Save acquisition method	no	no
Save data analysis method	yes	no
Load/run/save sequence	yes	yes
Modify acquisition parameter	yes	yes
Re-Integrate chromatograms manually	only in batch review	no
Change integration events	only in batch review	no
Recalibrate overview and peak summing	only in batch review	no
Recalibrate other	no	no
Apply method to data and print report	yes	yes
User-independent automated result versioning	yes	no
Access to tasks with manual result versioning	no	no

Table 12
Comparison of user privileges in the ChemStation Plus Security Pack and the standalone ChemStation

Application security

The Security Pack only allows users with a given user-ID to log on to the ChemStation Plus application, as shown in figure 12. Users need to be set up by the administrator to gain access. At initial login, users must specify their initial password in order to keep it unique to each user. Protecting the application software from unauthorized access during operation is possible with a separate session lock (figure 17). This lock function offers

- an interactive session lock which should be enabled manually before leaving the computer unattended, e.g. during a break or shift change, and
- for enhanced security a time-based automated lock of the session for other periods of short-term absence from the computer.

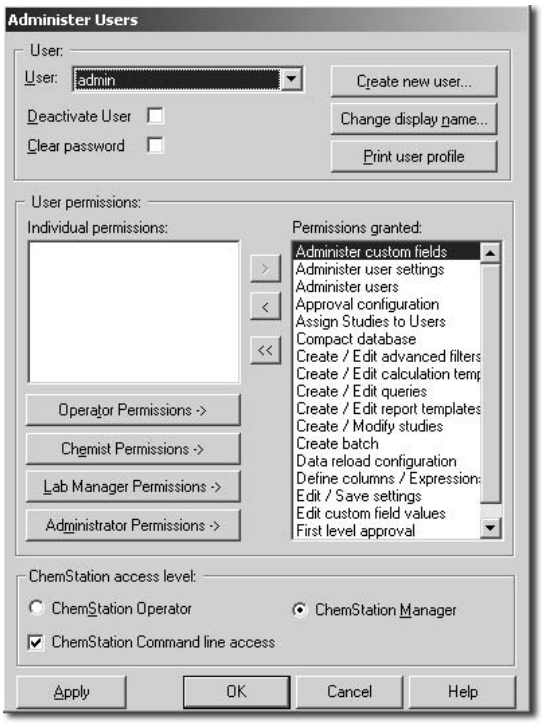


Figure 16
User Management in ChemStation Plus Security Pack

The time-based session lock is configured centrally through users with administrative rights in the ChemStore C/S database, and is automatically applied on all connected ChemStation Plus clients. The session lock allows to lock each instrument session individually and independently, so users sharing computers with two or more instruments connected to one computer can operate with a clear user distinction and unique user identification. The name of the current user and the instrument session are always shown in the title bar. The instrument sessions can be locked either

- privately, allowing only the user who locked the session or an administrator to unlock it, or
- non-privately allowing all users with a valid user-ID in the database to unlock the session, for example during shift changes (figure 17). If a dialog is still open the application will automatically lock privately.

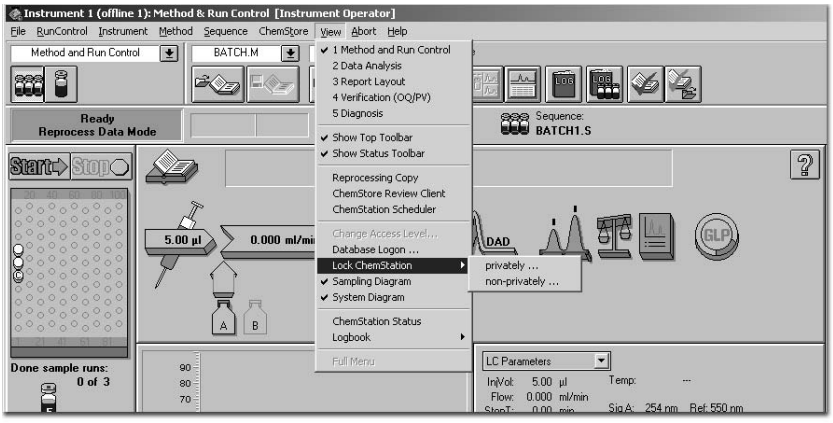


Figure 17
Instrument session lock

Data integrity

The Security Pack maintains full data integrity by storing all results along with the raw and meta data in a relational database as shown in figure 18.

Result revision management

Daily work in the analytical laboratory often requires sample reanalysis. The ChemStation Plus Security Pack includes a result versioning that stores all recalculation results from one original injection as result versions. In addition, the application software includes a tool that automatically detects new results during the reanalysis process. This application-controlled automated process does not require any user interaction such as *Save Results* or a similar action. It is completely user-independent and covers the following reanalysis steps:

- All functions in the batch review that calculate or change results such as reintegration, recalibration, method modifications (for example changing compound names) execution of predefined methods including manual reintegration
- In the data analysis view: Integrating, printing reports and recalibration excluding manual reintegration

Sequence reprocessing as well as all initial review tasks (loading a batch from disk, initial loading of a run into the interactive data analysis view) always create new result versions. These reanalysis tasks cover all activities of the ChemStation operator thus ensuring that all reanalysis steps at the ChemStation operator level include a user-independent versioning.

In addition, ChemStation Plus managers can perform manual result manipulation interactively in the *Data Analysis* view without using the batch review user interface. The user-independent revision management does not cover the manual reanalysis of results in the standard ChemStation data analysis view. The user creates new result versions in this review function using the manual *Transfer Data to Database* command (figure 19).

The following manual tasks in the Data Analysis view, outside of batch review, require a user selected *Transfer Data to Database* command to create a new result version:

- drawing a manual baseline,
- deleting a peak,
- tangent skimming of one peak,
- splitting a peak, and
- integrating manually with a negative baseline.

Access to tasks with a user-dependent creation of new results is the only difference in the result management between the ChemStation Security Pack manager level and the ChemStation Security Pack operator level. The new result version in the database is the same for both automated and user-dependent data transfer.

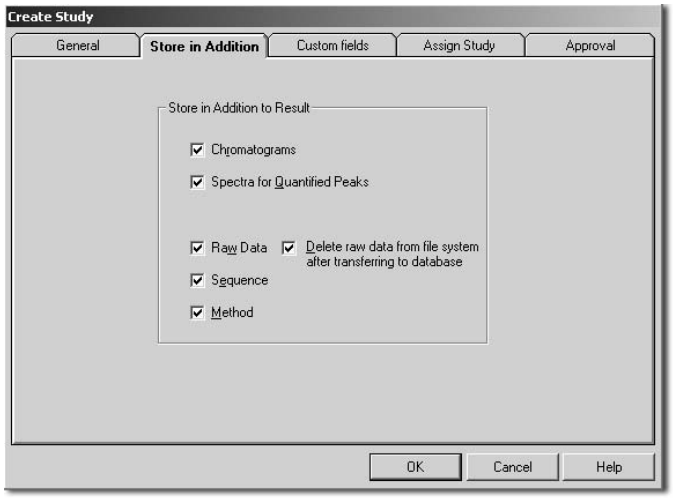


Figure 18
Default configuration of data storage in database

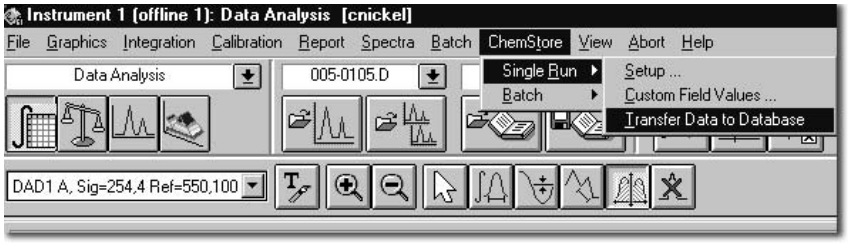


Figure 19
Manual revision management

User-independent, automated result version management

The data storage includes an application controlled version management that is based on the creation of a result reference file. Prior to reprocessing, the application software creates a binary result registry file called *save_sec.reg* for each file. This *save_sec* register is stored along with the raw data. It includes all numeric results of the current result revision in a binary format, such as amount, compound retention time and so on. Whenever a new result is calculated, the software automatically compares the new run result with the original result in the register file. If the results changed, the software detects the difference between the most recent and the current result and creates a new result version.

For proper documentation of the changes, the application software creates a second file in a human readable format that stores the results of the comparison and documents the changes. The file is named *sec_trac.txt* and is stored along with the raw data in the *.d subdirectory, as shown in figure 20. Both the registry and the text file are also stored in the database along with the raw data and they can be restored to disk with the data file, if necessary. These changes including manual integration events are also documented in the Manual Integration Events section of the ChemStore audit-trail as shown in figure 21. The audit trail as well as the sec_trac.txt can be used in order to regenerate the result from raw and meta data at any time, for example in an audit situation (see also the application note "Handling of Electronic records with ChemStation Plus" publication number 5988-9643EN, which is available under a confidentiality agreement).

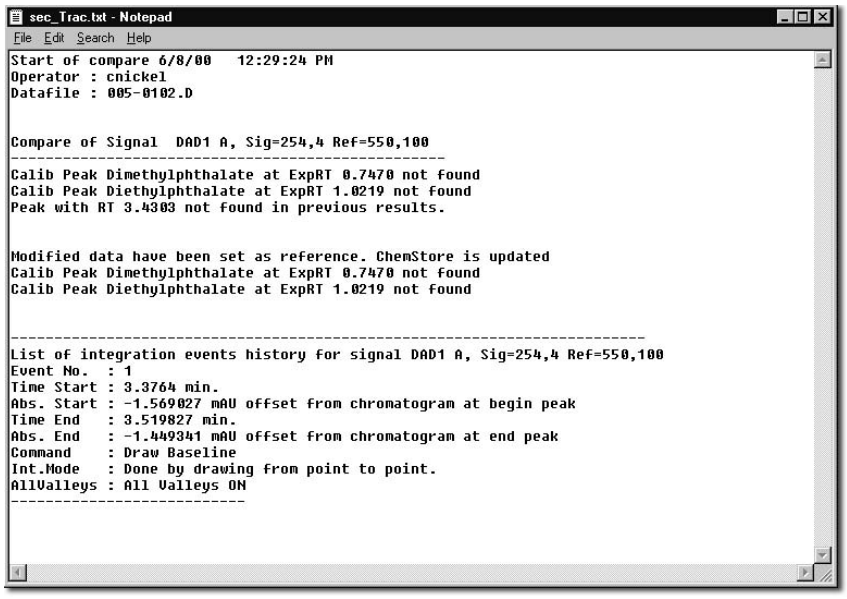


Figure 20
Text file documenting result changes for the actual run revision

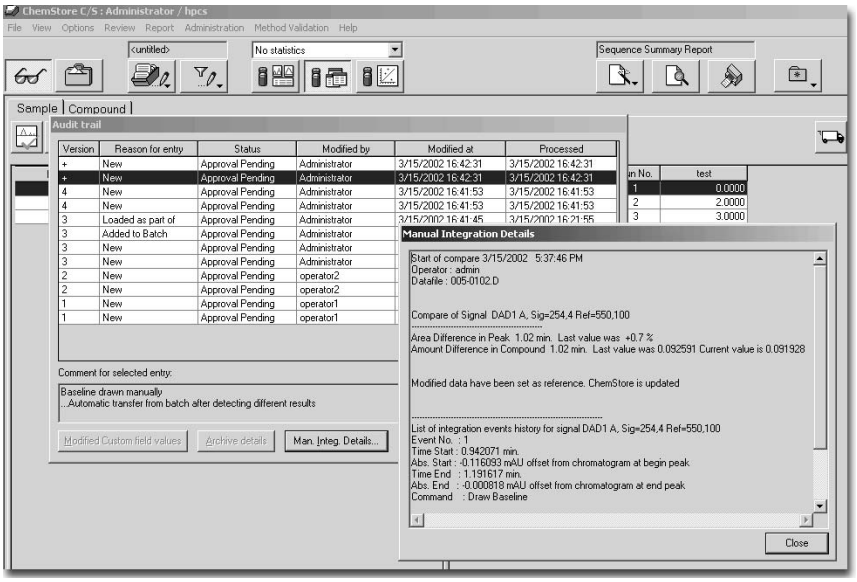


Figure 21
Manual integration events documented in ChemStore run audit-trail

Summary of version management in the ChemStation Plus Security Pack

Each time a new result is calculated in the ChemStation, the application compares the values with the result values of the last reprocessed result copy. If it detects a difference, it automatically initializes the data storage in the database. Each data transfer of new results creates a new version entry in the database so that no data is ever overwritten. The versioning also assures that no "data" is lost and that a complete "chain of events" is documented. This ensures full data integrity and traceability.

Agilent ChemStation Plus Security Pack—Graphical Result Review and Calculation

The graphical result review for example inspecting the baseline of the chromatogram or zooming in to check the integration, is done in the ChemStore review client. If any further rework is required the data is submitted to the ChemStation batch review user interface for data reanalysis. In batch review the ChemStation Plus Security Pack allows splitting the review into a working and a calculation section. The application allows a graphical rework of the chromatogram for each run that was included in the batch. This is done by setting new integration events and applying manual events such as baseline drawings and others without an immediate transfer to the database. The transfer is initiated automatically as soon as the user has finished his work and decides to calculate the results with the new settings by moving to the next run or starting an automated result recalculation (figure 22). As soon as new results are created, the result transfer to the database is performed either for the single run, or if starting an automated result recalculation, for all reprocessed runs. During the transfer of manually integrated data the user is prompted for a mandatory comment that is written to the results audit trail. The comment can be either a selection from a set of predefined comments or a free text or a combination of both. After finishing the data reanalysis and closing the batch review interface, the temporary files will be deleted from the local hard disk.

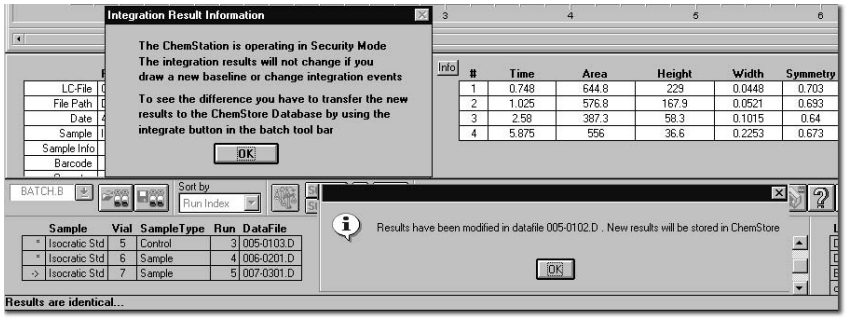


Figure 22
Result calculation and automated versioning

21 CFR Part 11 permits the use of electronic signatures if the application ensures data integrity, data security and full audit-trail documentation. If an electronic signature is supposed to be equivalent to a handwritten signature it must contain at least two distinct identification components such as an identification code and a password.

Approval of results

The ChemStation Plus Security Pack protects all activities that create, modify or delete electronic records with user privileges and electronic signatures. Signing for approval is a privilege that must be configured and granted by the system administrator and is therefore limited to certain users. Signing runs for approval or rejection always prompts for a re-identification and password confirmation of the signer for each run, plus a mandatory comment for the sign off, as shown in figure 23. The signer has to be the currently logged-on user.

ChemStation Plus provides three levels of approval tied to two separate user permissions to support the typical approval workflow in an analytical laboratory. It can be configured on a study level whether multiple approval levels should be applied or not. The approval configuration is part of the study settings. For new studies the settings from the global approval configuration template are copied to the study. The approval configuration is shown in figure 24.

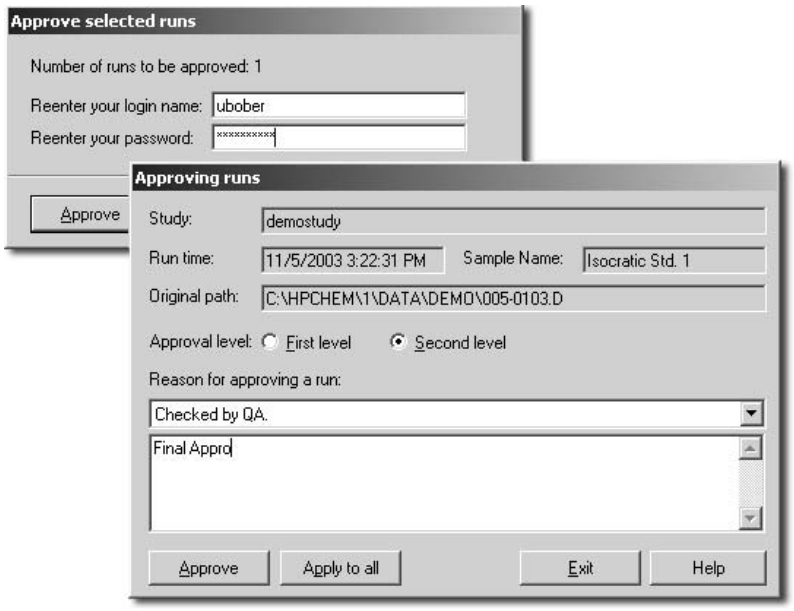


Figure 23
Signing off results requires reentry of user-ID with password confirmation and a mandatory comment

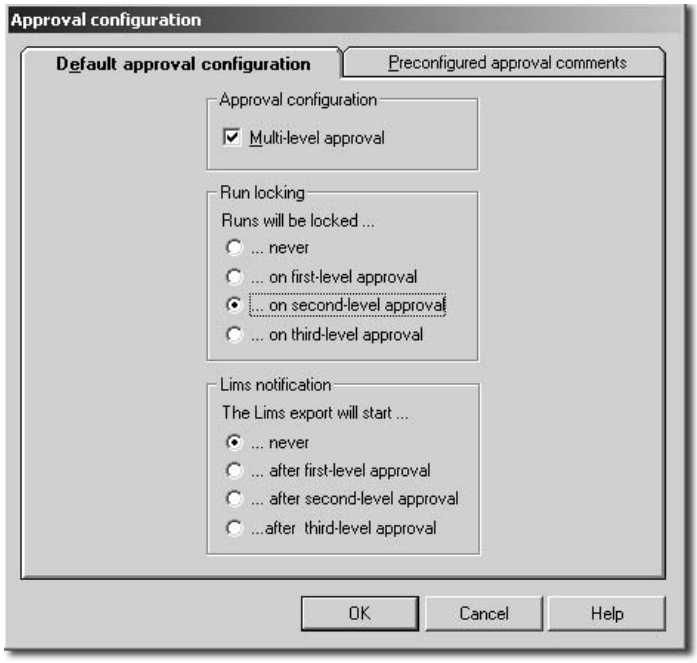


Figure 24
Global approval configuration template

The operator will typically give the first level approval when reviewing his results. To allow for peer reviews the application supports multiple first level approvals. The second level approval lies in the responsibility of the laboratory manager when signing off the results and prevents a signed run from further first level approvals, unless the run is rejected. The third level approval (equals a 2nd second level approval) can serve as the final sign-off by the quality control department. It requires the signing user to have the second level approval permission. After the third level approval no more signatures can be applied unless the run is rejected. Optionally runs can be locked from reanalysis after the approval (see figure 24). Which level finally locks the run is configurable. The administrator assigns the permissions for the different approval levels to the users.

Preconfigured approval comments

The ChemStation Plus Security Pack provides the ability to globally define approval comments. These comments consist of two components - a short fixed text that cannot be modified nor deleted by the signer and a pre-defined default text that can be changed during the signing. These two components appear during the approval. The signer has to choose a fixed comment from the dropdown list box containing the pre-configured comments as shown in figure 23 and can optionally enter or change the free-text comment. The approval comments are defined by the administrator in the global approval configuration template.

All other sensitive actions (for example, changing run-related custom field values such as the batch ID) and the archival or deletion of runs follow the same process as described above and are tied to distinct user permissions. All electronic signatures are noted in the individual sample audit-trail and in the database logbook.

The ChemStation Security Pack uses electronic signatures based on the application User-ID/password combination to uniquely identify the user and his or her signature. In order to keep the password unique to the individual user an additional security function is implemented to periodically check and revise passwords, and apply the company's password policy (figure 25). The administrator can specify the values for these conditions.

- Minimum length is the minimum acceptable length (in characters) of a password. Passwords shorter than the minimum length are invalid and rejected by ChemStore C/S. The default is eight characters with a valid range between 0 and 30.
- Password expiry date is the number of days over which the password remains valid. The password expires after the specified validity, and a new password must be provided. The default is 90 days with a valid range between 1 and 32000.
- Password uniqueness is the minimum number of new, unique passwords that a user must use before a password can be re-used. The default is 12, which means that a user must change the password at least 12 times before re-using the original password. The range is between 0 and 32000.
- Account lockout after 'x' attempts (where 'x' is the number of failed log-on attempts) is the maximum number of consecutive unsuccessful attempts that a user can enter before ChemStore rejects the user. The default is three with a valid range between 0 and 32000. If the maximum number of re-entries is reached, the current user is invalidated and must be reactivated by a user with the required permission.

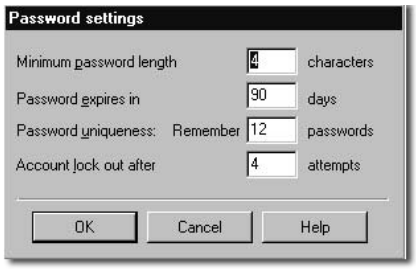


Figure 25
Password policy

The Agilent ChemStation Plus Security Pack includes four audit-trails:

- run logbooks,
- method revision history data,
- sample audit-trail, and
- database logbook.

Run and sequence logbook

During data acquisition, all events are documented in the sequence and run logbooks with date and time stamp (figure 26). The sequence and run logbook documents all data acquisition events such as

- start and execution of methods
- the actual sequence line in the sequence table,
- any failure during method execution, and
- any modification of method parameters during the analysis, such as manually extending the run time
- initialization of data spooling to the ChemStore C/S database.

Method changes

The method changes are stored with each current method version including a mandatory user comment for the change (figure 27). The method audit-trail stores

- the time of change and the operator who performed the change
- the current method revision in the database, and
- a mandatory comment of at least five characters each time the method was changed.

Sample audit trail

The sample-related audit-trail, shown in figure 28 documents

- all changes and modifications, on one sample,
- all run versions,
- all user comments during reanalysis cycles, and
- a detailed change documentation of manual integration events.
- all approval events including the name of the approver, date & timestamp, approval comment and the level of approval.

All reanalysis events and result versions are documented in the sample audit-trail. The sample audit-trail creates for each result change one new line in the audit-trail table. It displays both the interactive manual changes and the system generated entries each in a separate line. Examples for

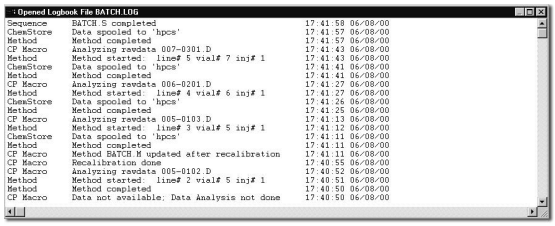


Figure 26
Run and sequence logbook

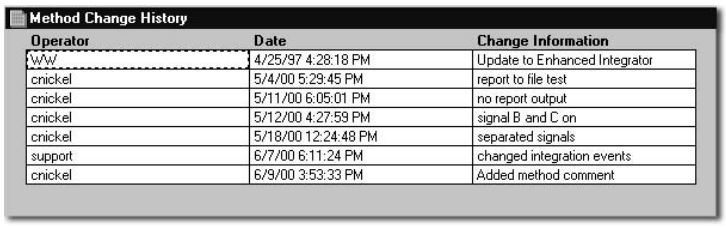


Figure 27
Method change audit-trail

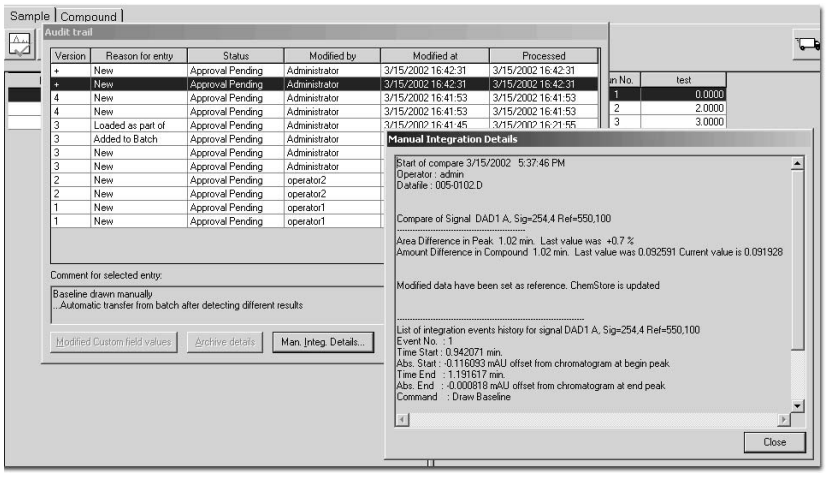


Figure 28
Audit-trail table with manual change documentation in the comment field

manual interactive changes are:
- change of custom field values
- manual reintegration during reanalysis,
- approval, rejection and retransfer to batch,
- reloading data to disk,
- archiving and dearchiving, and
- re-opening of read-only runs.

The automated entries in the sample audit-trail are created when
- a run is transferred to the database
- a new result version is created
- a run is reloaded in the ChemStation batch review interface for reanalysis.

Database logbook

The database logbook (figure 29) stores all application related activities such as:
- log-on/log-off events and failed logon attempts,
- archive/delete/reopen activities,
- session locks and unlocks,
- approval and rejection of runs,
- modification of custom fields and custom field values,
- changes in user administration,
- modification of user permissions,
- password resets and password clearance, and
- database migration from Access to Oracle.
- Account lockout events.

Review of method parameters

Each result version is associated with its ChemStation method that is stored in the relational ChemStore database. To inspect the differences in method parameters between result revisions or to review a method that was used to generate a specific result the application provides direct access to the method information from the ChemStore user interface. All method parameters, including acquisition parameters, data analysis parameters and calibration information can be reviewed in read-only mode as well as printed. The method report header contains information on
- the associated result version,
- method name,
- method modification date,
- study name,
- database name,
- sample name,
- injection date and
- acquisition instrument.

Changes to method parameters can only be applied in the ChemStation. For this purpose the method has to be restored from the database. New result versions generated with the modified method are spooled to the database along with the method.

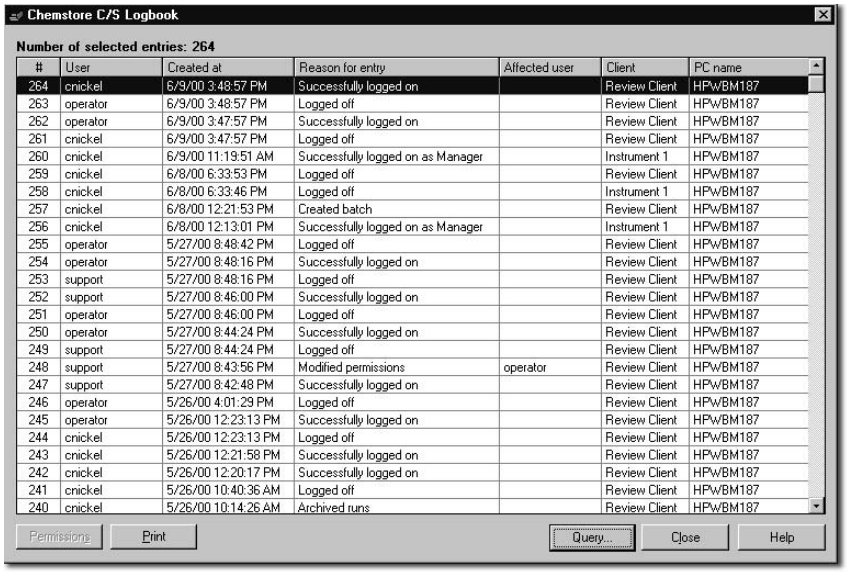


Figure 29
Database logbook

The email notification feature (client-server only) allows to send an email to a configurable list of recipients on the event of

- account lockout
- batch submission
- user permission change
- user creation

For each event the recipients can be defined separately as well as a user-defined message text and subject.

This function requires an e-Mail server to be running in the network. The e-mail message can be transferred to the e-mail server through Simple Mail Transfer Protocol (SMTP). For example this can serve for the purpose of instant notification on unauthorized attempts to access the database. An e-mail message can be triggered by account lockout events in the ChemStore C/S database logbook. (figure 30).

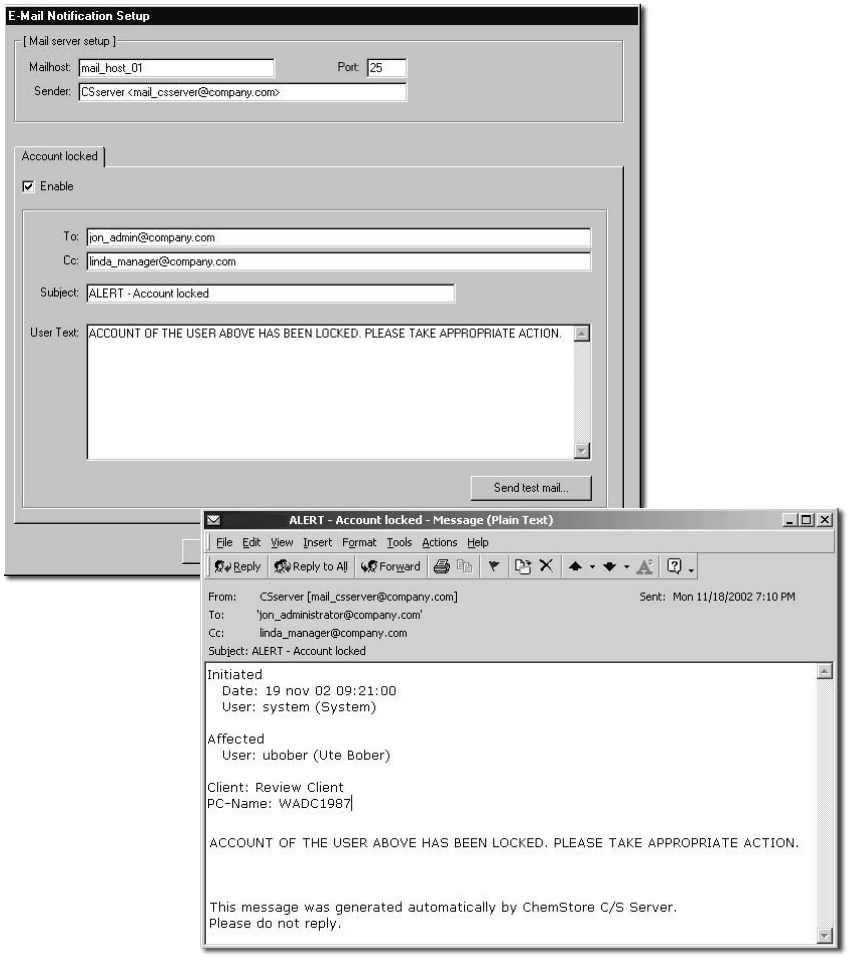


Figure 30
Setup of e-mail notification

ChemStation Plus Security Pack—Product Options and Configuration

Standalone version

The standalone version provides the ChemStation CD-ROM revision A.10.01 or higher and the ChemStation Plus CD-ROM revision B.03.01 or higher as described in the table next to this text.

Description	Product No.
ChemStation Plus Security Pack. Adds the secure ChemStore C/S relational database add-on software module to the ChemStation Plus SW for A/D, GC, CE, LC and CE/LC-MSD. Supports 21 CFR Part 11. Includes user documentation, licenses and media.	**G2183AA** 1 per PC 1 per laboratory
License to use G2183AA on another PC. Includes license and user information only. Supports 21 CFR Part 11. Must be on same order as G2183AA or requires a valid license for G2183AA.	**G2187AA** 1 per PC be in the same laboratory
ChemStation Plus client upgrade software. Upgrades a single ChemStation Plus client to the latest software revision. Requires valid software licenses and ChemStation upgrade software G1656A.	**G1657A**

Client/server version

The client server/version of the product consists of a set of components that are required to implement ChemStation Plus Security Pack in a client/server version. The product number are listed in the table next to this text along with the required quantities.

Description	Product No.
ChemStore C/S server application software. Includes:1 x ChemStore C/S and Oracle 9i standard edition software, 5 Oracle application-specific named user licenses are included.	**G1410A** Qty: 1 per server
Oracle named user license for Agilent NDS Required for each named user of the ChemStore C/S server database.	**G1411A** Qty: (number of clients connected to server) – 5
ChemStation Plus Security Pack. Adds the secure ChemStore relational database add-on software module to the ChemStation Plus client server SW for A/D, GC, CE, LC and CE/LC-MSD. Supports 21 CFR Part 11.	**G2183AA** Qty: 1 per server
ChemStation Plus ChemStore client license. Includes one online ChemStation Plus license for online data acquisition and one ChemStore C/S offline data review license. Includes license and user information only. Requires but does not include ChemStation Plus software media.	**G2186BA** Qty: (number of clients connected to server – 1
License to use G2183AA on another PC. Can be used as additonal copy for standalone installations or as additional Security Pack client in ChemStation Plus Security Pack C/S installations. Includes manual, 1 license for either online or offline use and media. Supports 21 CFR Part 11 Must be on the same order as G2183AA or requires a valid license for G2183AA.	**G2187AA** 1 per PC in the same laboratory.
ChemStation Plus client upgrade software. Upgrades a single ChemStation Plus client to the latest software revision. Requires valid software licenses and ChemStation upgrade software G1656A.	**G1657A**
ChemStation Plus server upgrade software. upgrades ChemStation Plus server software to the latest revision. Includes G1656A ChemStation software upgrade. Requires valid software license.	**G1655BA**

4. Agilent ChemStation Plus Method Validation Pack

Introduction

A comprehensive understanding of the functionality of Agilent ChemStation Plus Method Validation Pack requires a brief introduction to the general aspects of method validation.

The goal of method validation is "to provide documented evidence that a specific process will consistently provide results meeting the predetermined specifications." This definition is taken from one of the FDA's method validation guidance documents. In other words method validation is the process of evaluating and documenting the performance of an analytical method to ensure that the method is suitable for its intended use by ensuring compliance with product or method requirements. The outcome should provide sufficient confidence in the result produced with a particular method.

The analytical purpose of the method validation experiments is to provide a master method with a master chromatogram for all consecutive separations of this particular sample. Method validation testing must compare results of multiple runs (it is inter-chromatographic) in order to answer the question "is this method suitable for the separation task?" The comparison must give a qualitative and quantitative answer to this question based on the analytical results. A comparison typically involves a human judgement, so how can a comparison provide a user-independent and quantitative result? This is the most difficult task in the method validation process, because proper execution requires:

1. The definition of general good quality criteria for a method to address the qualitative requirements, and
2. The definition of specific requirements for the individual analytical problem to address the quantitative question.

Eventually it requires an answer to the question "does this method provide good results based on independent requirements?"

For step 1, ICH and FDA used the definition of general good quality criteria (along with many other contributors). These organizations defined a number of criteria that a separation method must fulfill to be classified as "good quality." These criteria are

- accuracy
- precision
- robustness/ruggedness
- selectivity
- limit of detection/quantification
- linearity
- calibration function

Based on the compound type, all or a subset of these criteria must be met. Most common compound types are

- main compound
- side compound
- known impurities
- unknown impurities

It is obvious that it is not necessary to determine the limit of detection for the main compound as the amount of the main compound will always be closer to saturation than to limit of detection. A detailed list of compound types and appropriate test criteria can be found in ICH and USP literature. Method Validation Pack uses built-in templates to automatically configure the method validation according to the guideline under consideration. The ICH has also published a guidance on "Stability Testing in New Drug Substances and Products" to define the required amount of information and procedures for the submittal in a registration application for products (ICH Topic Q1A). The purpose of stability testing is to provide evidence on how the quality of a substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the substance, and recommended storage conditions. Method Validation Pack does include tests for short-term and long-term stability testing according to the ICH guideline.

Based on these test criteria, step 2 can be executed. This is an individual definition of requirements (quantitative limits) for the statistical results of the tests by the responsible validation person. This step must be repeated for each new validation and will require different limits for each validation experiment. Method Validation Pack maps this step with a set of advanced statistical calculations. The calculations offer simple summary statistics (RSD, %RSD and linear regression statistics) as well as a set of advanced calculations for outlier detection, trend tests and many more. For each criterion, a different set of statistical calculations on the result values is performed based on the test requirement. The administrative user defines the calculation limits, transferring analytical requirements into

quantitative result criteria. Method Validation Pack offers tests such as Neumann trend tests and Outlier tests (e.g. according to Dixon) and many more to provide and document an assessment of the quality of analytical separations.

Method validation is an iterative process. Through the course of the validation it might turn out that some acceptance criteria need to be revised or even that the whole method of analysis is not suitable for solving the analytical problem. To support this approach Method Validation Pack allows to generate and manage multiple versions of the same validation.

Step 3 is to construct the overall validation report including the validation data, results and statistics, graphics and additional information such as required standard operating procedures for sampling, analysis etc. Method Validation Pack includes a variety of different reporting functions.

What's New?

With the latest revision users can benefit from new functionality in many areas as listed below.

Validation planning

- Solution stability calculations for short-term as well as long-term stability studies (see *ChemStation Method Validation Pack — Checkpoint Planning* on page 52)
- Enhanced handling of selectivity data and calculation (see *ChemStation Method Validation Pack — Checkpoint Planning* on page 57)

Validation execution

- Submission of custom validation sequences (see *Working with ChemStation Plus Method Validation Pack — Level 3: Checkpoint planning* on page 49)
- Partial execution of validation sequences (see *ChemStation Plus Method Validation Pack — Interaction with other ChemStation* Plus *modules* on page 58)

Validation report

- Calculation formula documented in the report
- One-page summary report
- Optionally color-coded test results in the reports
- Manual integration indicator in the report
- Optional inclusion of audit trail information in validation reports
- Development validations carry a marker in the report (see *Working with ChemStation Plus Method Validation Pack — Level 1: Reporting* on page 51)

Export

- Export of validation reports in pdf-Format (see *ChemStation Plus Method Validation Pack — Data Security* on page 62)

Administration

- Unlocking of locked validations with an electronic signature (see *ChemStation Plus Method Validation Pack — Data Security* on page 65)

User documentation

- Revised Method Validation Pack User's Guide and Online Help

Product description

Agilent ChemStation Plus Method Validation Pack is a data management system for all method validation data. It includes advanced statistical calculations and result management in a relational database. Method Validation Pack offers a compound-centric design. For each compound it allows to define a set of tests (checkpoints) according to ICH, Pharmacopoeia or DIN guidelines. By default each test requires results of at least six repetitive injections in order to use statistics for a quantitative result evaluation. In some areas less than six values can be used, but then some statistical evaluation methods are omitted. The statistical results can visualize whether the analytical results meet their specifications or show any deviation. When all tests are passed, the compound meets the requirements. When all compounds meet the requirements the method can be seen as applicable or "validated" according to its well-defined purpose and with the specified limits. At this stage, the validation can be locked, the full validation is printed and the validation study for this method can be archived.

Method Validation Pack provides all required statistical functions and calculations, stores all results with their raw and meta data, displays the statistical results graphically, and captures all actions in automatic user-independent audit-trails. Further, it allows to map the key steps in validation experiments - planning and definition of expected results, experiment execution and result evaluation - as separate tasks tied to different user permissions. All steps are documented in audit-trails and are fully traceable. Method Validation Pack is equipped with a fully featured document management system (DMS), that is used to retain and manage all versions of a validation (including all attachments). The DMS provides a powerful search engine, further complemented by the ability to tag validations with additional keywords.

Configuration

The configuration of validation experiments is hierarchical (figure 31). The top level represents the complete validation experiment. This level may include standard operating procedures (SOP) for sampling, sample preparation, description of quality and grades of solvents, testing materials, a description of the analytical method and so on. Such information can be directly added as validation comments or enclosed as document attachments to the validation.

The next level introduces a compound-centric view of the validation in the form of components. This enables individual calculations and validations for each compound or peak in an analytical separation. For further structuring the validation, it is even possible to define multiple components for the same compound or peak (for example if different matrix effects are investigated).

For each component, additional sub-levels offer a list of checkpoints such as robustness, linearity and others as defined in the various regulatory guidelines. The planning of checkpoints is the lowest level because each checkpoint can have a different planning configuration. Within the planning dialog, data is configured such as the determination method, the applicability of multiple injections, or multiple determinations for one result data point as well as the number of result values and test specifications such as nominal (expected) values or limits.

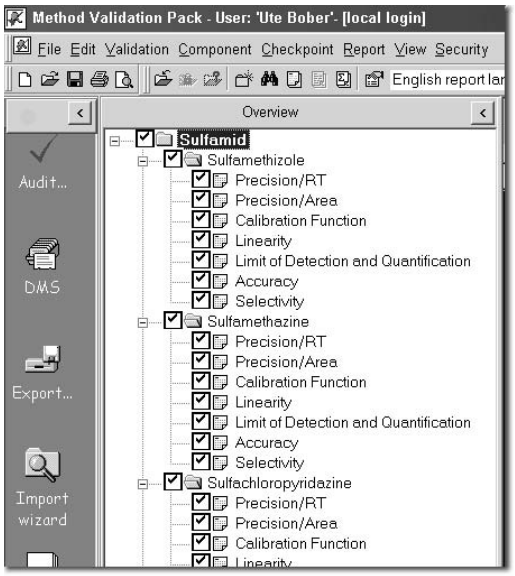


Figure 31
Hierarchical structure of a validation

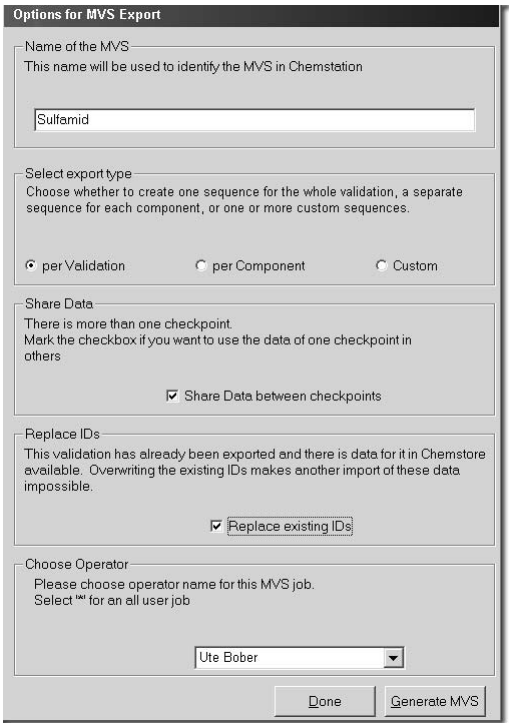


Figure 32
Options for generation of Method Validation sequence

Test execution

Having completed the validation configuration, the experiments can be executed on an Agilent ChemStation Plus system. Method Validation Pack transfers the theoretical validation planning into a list of analytical runs by creating one or multiple ChemStation method validation sequences (MVS). The user has three options during sequence generation. As shown in figure 32 the validation

can be transferred into

- a single sequence for the complete validation
- one sequence per component
- or a set of user-defined custom sequences.

The custom sequence option allows to define as many sequences as required in any combination of the invididual checkpoints. During the submission the sequence can be assigned to a specific owner or made available to all users.
To minimize the amount of necessary data and analysis time some checkpoints can share, if suitable, the same result data. This function can be enabled in the MVS export options (figure 32). For the ease of use Method Validation Pack provides a wizard that proposes which result data is suitable for sharing. The user may decide per checkpoint whether or not to share the result data as shown in figure 33. Method Validation Pack transfers these sequences to the ChemStation for data acquisition and data analysis. The sequences can load into an Agilent Method Validation Pack ChemStation system and run similar to other sequences in the Agilent ChemStation. The results of the method validation sequences are stored automatically in the ChemStore database. Each validation corresponds to a separate ChemStore study. If a validation sequence failed it can be resubmitted and rerun. Or if only parts of a validation sequence need to be repeated, for example due to an instrument error towards the end, it can be loaded into ChemStation and modified accordingly.

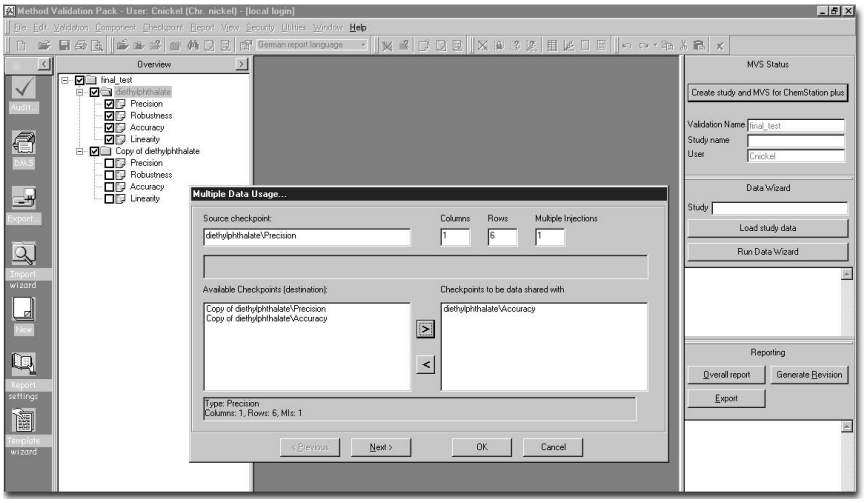


Figure 33
Wizard for multiple usage of checkpoint results

Result data entry and statistical calculations

After completion of the analytical experiments the results can be uploaded from the ChemStore database into Method Validation Pack. The upload from ChemStore is an automated direct database data access invoked by the user. The transfer is executed as defined in the planning of the validation experiments. The data wizard helps to find and complete data sections, that require manual entries. The analytical results are contained in the ChemStore database whereas the validation results are contained in Method Validation Pack. Traceability of results is achieved with unique run-IDs in ChemStore for each result version. The ChemStore run-IDs are also transferred and displayed along with the analytical results in the Method Validation Pack.

When all result data is imported, the validation report can be printed. This report displays all data related to the validation as defined in the top-level validation configuration. This includes the components, their planning and result data as well as the calculation results, statistical data and conclusions, for example, “outliers [not] detected” along with a graphical representation of the results in charts.

Data management and audit-trails

All configuration and result data along with the MVS files and validation reports form the “validation”. It is stored in a relational database for full data integrity and to ensure data security. Every validation modification or configuration change is stored in the DMS database as a new version of the existing validation. All changes and modifications are documented either in the program audit-trail (for program related events such as logon) or in the validation audit-trail. In a server-based installation all validation data is stored in additional Oracle tables of the same database instance as used by the ChemStore database. In the entry-level system each validation is stored in a separate validation database on the local hard disk (file extension .VDB).

ChemStation Plus Method Validation — System Requirements

Compatibility with ChemStation Plus modules

Agilent ChemStation Plus Method Validation Pack A.02.01 is compatible with the following ChemStation Plus modules:

- Agilent ChemStation for GC, LC, A/D, CE, CE/MS and LC/MS for instrument control and data analysis
- Agilent ChemAccess remote access and module
- Agilent ChemStore data organization and data storage module

For result management in a relational database, Method Validation Pack requires the ChemStore database or ChemStation Plus Security Pack. Method Validation Pack is available in a standalone PC-based version or as full client-server application. The standalone database file format adheres to a common standard, which is used by many other applications, for example, MS Access. The client-server version is based on an Oracle relational database.

Hardware requirements

The following list shows the minimum hardware requirements for the client application:

- 600-MHz Pentium III (Pentium IV recommend)
- 4 GByte of free hard disk space
- 128 MB RAM for single ChemStation instrument. 256 MB is recommended for best performance, for Windows XP the minimum requirement is 256 MB.
- 256 MB RAM for two ChemStation instruments (512 MB or more is recommended for best performance)
- Display: 1024 ∞ 768, small fonts, 65-thousand colors

Method Validation Pack installs and runs on the same instance of the Oracle database as ChemStore C/S and thus does not require a separate Oracle licence. For server hardware requirements, please refer to the server hardware requirements

for ChemStore on page 5.

Software requirements

- Windows 2000 Professional with Service Pack 4 or Windows XP Professional Service Pack 1a
- Agilent ChemStation revision A.10.01 or later
- Agilent ChemStore C/S B.03.01 or higher
- Microsoft Internet Explorer 5.5 or later
- Microsoft data access components (MDAC) 2.8 will be installed on your system. If you already use a later version of MDAC, or require for compatibility reasons a previous version, please contact your Agilent support representative for compatibility information.
- A printer must be installed and configured in Windows.
- The hard disk partition that is used for installation of Method Validation Pack must be formatted with NTFS.

Hard disk space

Standalone installation

Method Validation Pack needs approximately 40 MB hard disk space for the installation files. The validation database files (VDB) typically require 250–1000 KB each. The exact size strongly depends on the size of embedded graphics. If possible, use vector graphics (WMF-format) rather than bitmap graphics (BMP) to reduce the validation file size. Using large bitmap graphics in validation comments also has an impact on the DMS size. Hard disk requirements for the Oracle database are discussed in the following paragraph.

Client-server installation

The client-server version of Method Validation Pack is based on an Oracle relational database. The application supplies three pre-defined schemes for the database installation: small, medium and large. The databases are separated into multiple tablespaces for better performance and administration. In particular, the tables storing the validation data (comments can contain large graphics) and those reserved for the document management system (DMS) reside in larger tablespaces, optimized for the management of BLOB data (binary large objects). Table 13 shows the database sizes according to the configuration. VDB files are validation data files, the DMS stores all VDB file versions; changes to one VDB file are stored as a new version, new VDB files create a new entry in the DMS system. The required space for an individual VDB file was discussed in the previous section.

Database parameter have been chosen for unattended operation; tablespaces and datafiles extend automatically until their maximum file size has been reached. Nevertheless, you should keep in mind that frequent database maintenance and administration is necessary to ensure optimum performance and correct and secure operation (backup tasks, size checks etc.). Your database administrator may manually expand your database if necessary. There is no known database size limitation in Method Validation Pack.

	Small		Medium		Large	
VDB data	**Database**	**MB**	**Database**	**MB**	**Database**	**MB**
	Initial size	30	Initial size	600	Initial size	1200
	Maximal size	300	Maximal size	1200	Maximal size	2400
	File growth	15	File growth	30	File growth	60
	Comments		**Comments**		**Comments**	
	Initial size	100	Initial size	1400	Initial size	2800
	Maximal size	700	Maximal size	2800	Maximal size	5600
	File growth	40	File growth	70	File growth	140
DMS data	**Database**	**MB**	**Database**	**MB**	**Database**	**MB**
	Initial size	20	Initial size	500	Initial size	2000
	Maximal size	200	Maximal size	1000	Maximal size	4000
	File growth	5	File growth	25	File growth	100
	BLOBS		**BLOBS**			
	Initial size	180	Initial size	4500	Initial size	18000
	Maximal size	1800	Maximal size	9000	Maximal size	36000
	File growth	45	File growth	225	File growth	900

Table 13
Preconfigured database sizes for Method Validation Pack in a client-server configuration using an Oracle relational database

General software operation

Compatibility with Microsoft functionality

Method Validation Pack is a Microsoft Windows program and can be operated via mouse and keyboard in accordance with the Microsoft Windows standard. Users of Microsoft Windows programs should easily become familiar with operating Method Validation Pack.

Context menu

When working with Method Validation Pack, the right mouse button opens the context menu displaying your current program options. The context menu can consist of functions concerning a selected component, or the attributes of a graphic or a report. All functions of the context menu are also accessible via the main menu bar.

User interface settings

All settings that are changed in the menus or tool bars are recorded for the user and saved at the end of a session. They are automatically loaded during the users next login.

Navigation bar

On the left side of the screen, the navigation bar presents the most important top-level functions of Method Validation Pack. You can use this bar for directly selecting the

- program, default validation or current validation audit
- Document Management System (DMS),
- export dialog,
- import wizard for templates,
- new validation wizard,
- planning wizard,
- report settings (output formats, etc.), and
- security settings

Ease of operation

All important tasks in Method Validation Pack are accompanied by wizards to make it easier for the novice user to become familar with the main tasks.

Validation assistant

Method Validation Pack comes with an additional validation assistant that helps to configure and setup Method Validation Pack functionality. An administrator can configure the assistant to automatically start after each user logon. In addition, the wizard can be started interactively at any time. The assistant helps speeding up the operation of the software, and offers a quick and easy way to resume your work. The assistant offers the following options when started

- Creation of a new Validation
- Opening an existing Validation
- Opening the last Validation (per user)

The validation assistant guides the user through all configuration and planning steps in Method Validation Pack. It can be used either to create a new validation or to add a new component to an existing validation. It is accessible from the validation or help menu or via the context as described earlier.

Data completion wizard

Some checkpoint information (such as the concentrations for linearity) can only be added after data acquisition. It is not available during checkpoint planning. Method Validation Pack therefore has an integrated data completion wizard. As long as a checkpoint is not complete, the related report cannot be generated and is flagged incomplete with an invalid-data entry in the table of contents. The Data Wizard points the user to all incomplete checkpoints prompting him for completion. Double-clicking it opens the data input grids. Input fields with a dark background are locked and supposed to be automatically populated with data from the ChemStore study. Input fields with normal background color require manual entries.

Application structure

ChemStation Plus Method Validation Pack translates the validation requirements into a structured workflow following a stepwise approach to analytical method validation. It requires the user to thoroughly configure and plan a validation before executing the actual experiment. By design it forces the user to separate method validation testing into three steps:

- planning and design,
- test execution (run samples), and
- result calculation based on the experimental result data.

All of these tasks are managed within ChemStation Plus. All ChemStation Plus modules support data security, data integrity and audit-trails for comprehensive support of FDA's requirements for electronic records and electronic signatures (21 CFR Part 11). The combination of audit-trails in all ChemStation Plus modules with the advanced data security features built into the relational database offers full traceability and complete documentation of all steps during the method validation experiments.

Method Validation Pack hierarchy

The Method Validation Pack software structure is strictly hierarchical, divided into five levels. These levels also correspond to user-access levels. The list below outlines the step-by-step execution of the method validation experiments with the hierarchical structure and the user access levels.

Before acquisition – creating a validation template

1) Setup and configuration (User levels 5 and 4)
Overall validation planning, definition of program defaults and component configuration in the Method Validation Pack software

2) Checkpoint planning (User level 3)
Each checkpoint can use different calculation methods depending on the applied guidelines. The checkpoint configuration step is either repeated for each checkpoint or it is copied from another component using drag and drop functionality.

Data acquisition – the validation experiment

3) Experiment preparation, data management and execution (User level 3)
This step consists of:

- Creation of new or update of existing ChemStore study for the analytical result data
- Automatic translation of the validation into one or more system-generated ChemStation sequences based on the validation configuration and
- Submission of the sequence(s) to the ChemStation for data acquisition

After acquisition – the validation report

4) Data completion and result calculation (User level 2)

- Review of the data, that was acquired and stored in the corresponding study in the ChemStore database,
- Loading of the result data from the database into the Method Validation Pack, and
- Completing the necessary manual entries with the data completion wizard.

5) Creating the method validation report (User level 1)

- After data completion, the method validation report is compiled according to the report configuration in step 1 (style and level of detail, for example charts, statistical details, calculation formula)

Figure 34 again illustrates the steps outlined above. All configuration and transfer steps are fully automated and integrated with the other ChemStation Plus modules. All data transfers are automatic and documented in audit trails thus avoiding any accidental transfer or transcription error.

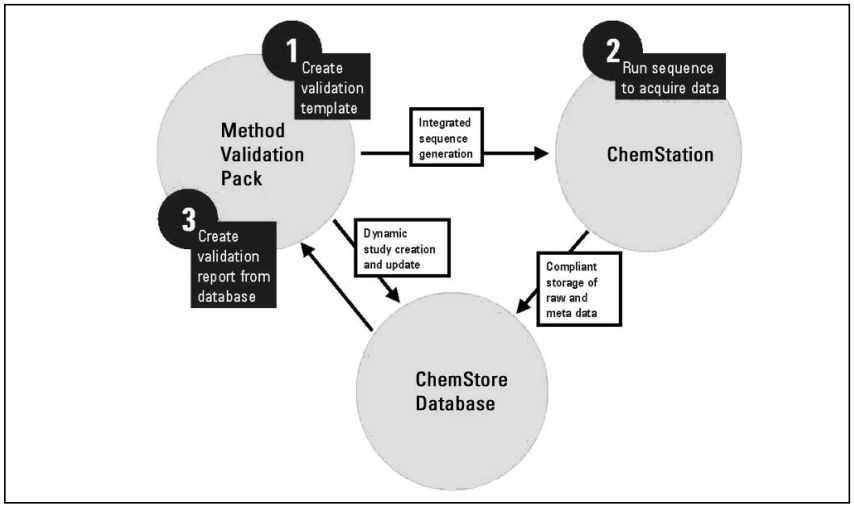


Figure 34
Interaction of ChemStation Plus software modules and their mapping of the key steps of method validation experiments

User levels

Top-level (Level 4 and 5): Validation setup and configuration

Setup
Method Validation Pack organizes data in method validation databases. A method validation database is the top-level container for all data that relate to one validation. All settings are linked to one validation database. For new validations the software offers a master validation template that allows building new validations based on the template. The following settings or properties are configured per validation (figure 35) and can be preconfigured in a template:

- validation configuration,
- output settings,
- default reporting header data,
- storage of external documents and,
- storage of method in text format.

Validation configuration
The validation configuration defines the parameters for the statistical calculations in the report. Each checkpoint offers different calculation options and is configured individually. For example the user may decide which level of significance should be applied for the t-values for the t-test as part of the selectivity checkpoint (default is "5% two-sided"). In addition, the configuration task defines overall calculations that are common for all checkpoints. These include outlier tests, trend test, homogeneity tests and systematic error detection. Other settings allow specifying the minimum sample size for each test, handling of zero as input value and handling of missing values.

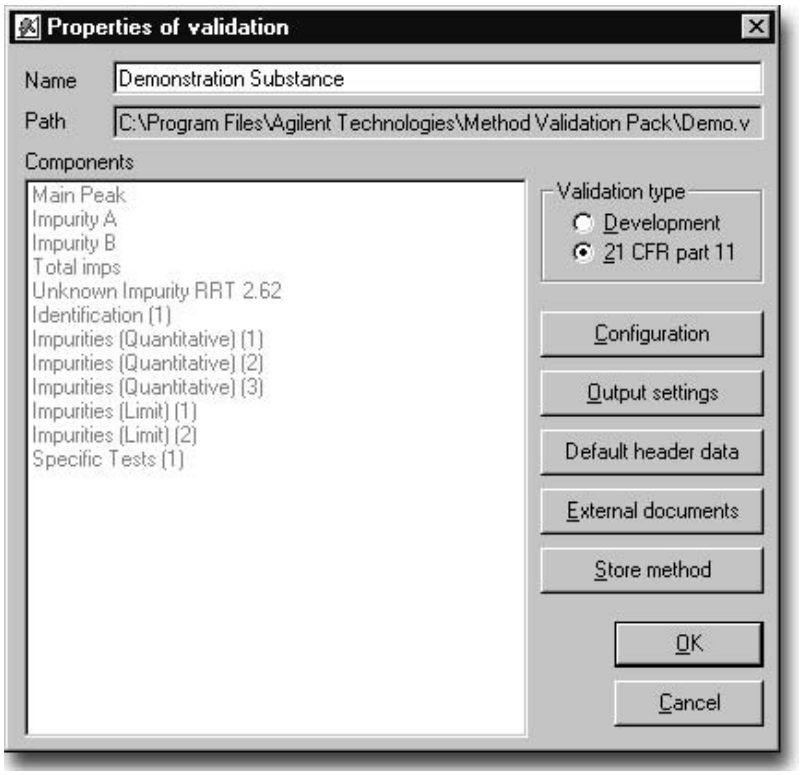


Figure 35
Validation properties menu for validation setup and configuration

For non-Part 11 validations ("development validation"), the user may also specify the audit-level in the configuration.

Output settings
The method validation output settings define the output format and content of the validation report. For each checkpoint the extent of statistical information contained in the report can be configured separately. For details on the checkpoint content, please see the checkpoint section lateron. Further, output settings define the decimal precision for the result data shown in the report as well as graphic settings, text elements, and whether or not to document the configuration values in the report or include audit trail information.

For text elements the output settings define:

- the report title page,
- an additional general report comment page,
- the report header
- additional footer text, and
- default comments for validation planning and validation configuration

In addition, the text configuration defines the checkpoint table headers. Each checkpoint can have up to ten freely configurable header data items with different user-defined content. The header information is used to describe general validation information that is necessary to uniquely identify and characterize the method validation experiment. Examples for useful

table header are the product name, the analytical equipment, QS or internal ID number, test method and others. Default entries for the header data can be defined when selecting the default header data button in the validation properties. Figure 36 shows table headers and default header data.

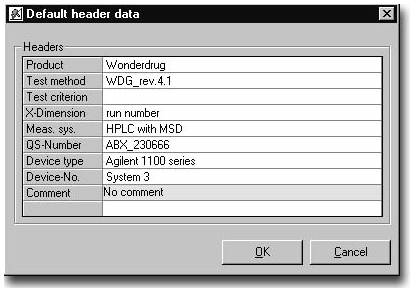


Figure 36
Default headers (grey) and header data

Table headers can only be changed or overwritten by changing the complete validation configuration while the default header data can be overwritten for every checkpoint.

The graphics section defines the checkpoints that will have graphic result visualization in the final report.

Default (checkpoint) header data
This section defines the header data section of the checkpoint report as defined in the output settings. It provides a single entry point for common data for all checkpoints e.g. the method name or an internal code for the tests. All data that are entered as default reporting header data are copied to all checkpoint headers. The default checkpoint header data can be manually modified for each individual checkpoint if the actual information are different from the preconfigured header data. Using default header data speeds up the checkpoint configuration as it allows skipping multiple data entries for the checkpoint headers. One example that might outline the usage of default data for the checkpoint header is the definition of the analytical system as checkpoint header. The system will remain the same for all checkpoints except for the ruggedness testing where another system from a different vendor might be used. The user now enters the analytical system by default in the default header data and applies this to all checkpoints. For the ruggedness checkpoint the default header data for the instrument will be manually overwritten, for all other checkpoints the default header data are copied and do not need a manual entry.

Storage of external documents
Users can store any external document with the validation. The document must be available as a file with an extension that allows direct read-out and data display. This is particularly useful for adding master methods, sample preparation and other method related information to the validation. During printing all external documents can be integrated into the final validation report. The storage capability of external documents in the method validation database allows using the Method Validation Pack software as a container for all method validation related data (see also the section on the DMS on page 62).

Store method
Store method allows adding the method as a text file to the validation database. The method must be in file format and can not be a folder or anything else that can not be opened with a standard editor.

Level 4: Component configuration and checkpoint configuration

The next level under the top-level is the component level. The component typically relates to a peak (or in ChemStation terminology to a compound) in a separation but it allows having multiple components for one peak e.g. to perform result comparison or result copies. Usage of multiple components per peak is mainly used during method development. During component configuration the user may specify a unique name for the component along with the checkpoints that will be executed for this component. Checkpoints are either created according to a user selection or can be based on predefined templates. The templates include:

- Complete range (all check points will be selected),
- Trace method (selecting precision, calibration function and limit of detection/quantification),
- Trace method with demand (above plus lab capability)
- Non-trace method (precision only), and
- Non-trace method with demand (above plus lab capability)

Each component typically includes one or multiple checkpoints from the following list:

- Precision - used to monitor random errors
- Robustness/Ruggedness
- Lab capability (mainly used in non-pharmaceutical applications)
- Calibration function
- Limit of detection/quantification
- Accuracy
- Selectivity
- Ring experiment (used to compare results among multiple laboratories)
- Linearity

The checkpoint configuration will typically depend on the compound type, and hardly any component requires execution of all checkpoints. The system therefore requires running the checkpoint configuration for each component individually.

Level 3: Checkpoint planning

Each checkpoint must be configured. The configuration defines the test and calculation methods, data sources and data types for x- and y values (e.g. for linearity x-value is amount in mg/mL and the y-value is peak height). A typical planning dialog, in this case for accuracy is shown in figure 37. The following sections are configurable for all checkpoints:

- **Headers**
  These data sections will show the default data if configured in the validation properties and allow individual data entry for each header line
- **Planning data**
  Selects the calculation method from a pool of possible calculations available for this checkpoint
- **Number of samples and y-unit**
  Defines the number of independent samples used for calculations (*Note:* By default, minimum number must be six and the system will show missing values either as Zero or as MV in case the configuration allows 0 as valid data input). Each sample translates into a separate sequence line and thus sample vial.
- **Multiple injections or determinations**
  "Multiple injections" means repetitive injections from the same vial and averaging the results before applying statistics; the number of injections can vary between 2 and 10. "Multiple determinations" allow using data from two or more different vials for the same checkpoint. Number of multiple determinations allows for values from 2 to 10
- **ChemStation Plus Method Validation Pack – Planning**
  In this planning area the user configures the ChemStation result data type for the checkpoint calculations. For example for precision data the calculation can be either based on peak area or peak height as determined by the ChemStation. Additional header information can be imported from ChemStore along with the result values. Available result values are peak area, peak height, peak width, retention time, and amount. For the selectivity checkpoint, resolution data is obtained with different calculation methods as provided by the ChemStation (tangent method according to USP/EP/ASTM, halfwidth method, sigma method, statistical method). Additional header information can be:

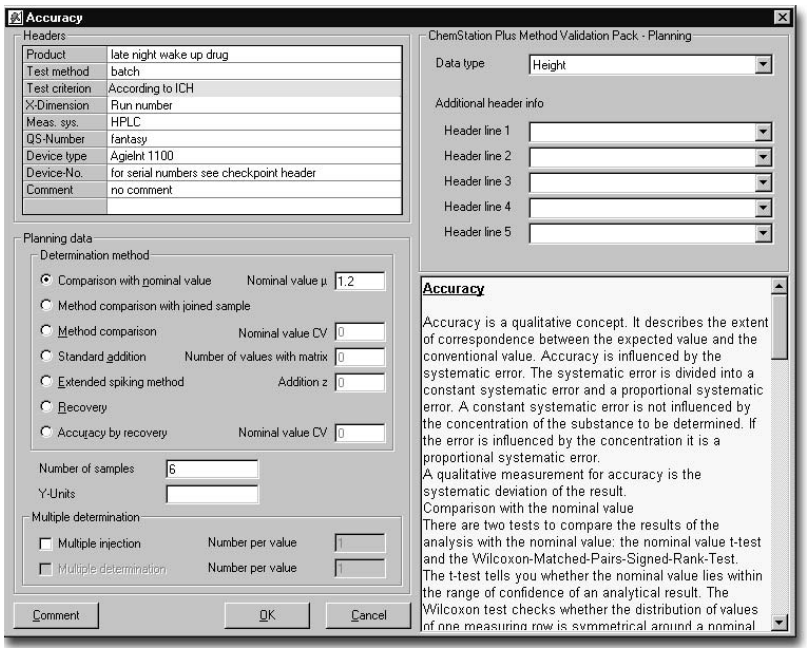


Figure 37
Checkpoint planning window (example for accuracy) with sections for checkpoint header data, test planning data, number of results y-units and multiple determination.

- study name,
- method name,
- method text,
- instrument name,
- instrument module with serial numbers,
- run Ids (database Ids),
- run Id with version number,
- run Ids and approval status,
- run Ids and raw data file path, and
- all custom fields with data entries.

The system allows a maximum of 5 additional header items providing information from the ChemStore database.

After the planning phase is completed the planned validation procedure can be automatically translated into one or more ChemStation sequences. Method Validation Pack provides the ability to submit a sequence

- per validation,
- per component, or
- as a number of custom sequences

to the ChemStation.
When choosing to create a sequence per validation, the software generates a single sequence containing all necessary sequence lines to complete all tests in one sequence. This will be the most suitable and efficient way in case the method will not be transferred between instruments and thus no ruggedness testing is required, or if no time-consuming tests are involved such as long-term stability. If a validation is structured per component in a way that each component can be validated in a separate sequence either on the same or a different instrument, sequences can be submitted per component. Method Validation Pack then creates a sequence for every component.
Depending on the number of compounds and the extent of validation it might be useful to define your own set of validation sequences. For this purpose the custom sequence submission provides the user with the capability to freely combine tests into as many sequences as required. For this purpose all tests are displayed in a tree-like structure, where checkpoints that include several data series are already divided into separate sub-items. The user can choose from the tree, which tests are to be combined in a sequence and submit the sequence. To make it transparent to the user, which checkpoints were already submitted, these are immediately highlighted in green.

The number of necessary experiments can be further reduced by the ability to share data between checkpoints, for example by using the same data set for more that one test, like for example reusing linearity data for the calibration function checkpoint. Data sharing is defined during sequence submission, where the software automatically offers all available choices that would allow data sharing due to the same data structure.

Level 2: Data input

After checkpoint configuration and planning is completed, users can start with the data entry. This is the first step involving experimental result data and following the planning phase.

Method Validation Pack offers three types of data input:

1. Automated data upload from the ChemStore database. Users select to load study data from the ChemStore study created for the validation and all data are automatically imported as configured in the planning phase and described in the previous section
2. Data import for all result data that is not created by the ChemStation and managed in the ChemStore database e.g. data from non-Agilent instruments generated during ruggedness testing. The system comes with an import filter function allowing for an automated data import. For details see the separate section on data import below
3. Manual data entry - for all data that are not created on a computer system, e.g. pH values, the system allows for a manual data entry

Data import
Data import uses an import assistant, which helps users to import data from external result summary files, typically in spreadsheet formats. It imports various file formats such as CSV, TXT, Microsoft Excel and any other ASCII formats

where the file extension has to be specified if it differs from ASC or TXT. The import assistant displays a definition dialog enabling Method Validation Pack to automatically load this summary data to its data input grids. The following definitions can be made:

- name and description of the import mask,
- source type (file extension) and path,
- field separator (delimiter),
- row options,
- data positions allowing to exclude header and text data (with optional transposition of the data), and
- column information (X-Y data, information for multiple injections and determinations).

The import settings can be saved as import mask and applied at any later time to import data. The system can handle multiple data import masks allowing to quickly import results from various data sources.

Level 1: Reporting

Method Validation Pack software offers multiple reports. Users can have

- planning reports–print all data from the planning dialog,
- graphics report for each checkpoint–prints only results in graphic representation,
- complete reports on checkpoint level, component level, and
- complete validation reports with all validation settings and all component and checkpoint results.

The validation report includes the following parts:

- Page header and page footer (Footer includes printed user name, date, page # of # and a signature placeholder for manual report sign-off.)
- Report title page
- Default comment page
- Table of contents with page numbers
- Checkpoint sections for each checkpoint consisting of header data, planning comment, experimental results, graphics and statistical results, execution comment and revision information from the document management system.
- Optional inclusion of the calculation formula for each checkpoint with a short explanatory text and a complete legend of the variables and symbols. This function is enabled on a global level via the report options as part of the program options.
- validation audit trail (optionally)
- a flag in the footer of the report indicating that the validation was done with a reduced level of audit trail (*development validation*, see page 47)

Available report styles
Method Validation Pack offers two report types:

- Normal report - standard report containing detailed information
- Short report - compact report containing only the most important sections and omitting for example statistical details

Both reports can be compiled in two different styles:

- Classic report - standard report look
- Modern report - different appearance using color-coded results (passed/fail)

Finally the software offers a concise summary report providing a one-page summary of the complete validation results. It contains only the checkpoint names and the test result (passed/fail statements).

Report customization
The following elements can be configured within the Method Validation Pack application:

- report language: German or English,
- report fonts and sizes,
- graphics section: line style, background color for data, color of axis and display of limits, axis annotations, and
- text sections: title page, validation comment page, report header and default planning and execution comment. All text sections can also include graphics such as company logos.

Method Validation Pack uses a Microsoft-Word-based reporting engine. If further customization is required it allows to open the entire method validation report as a MS Word document. This allows for easy data export of the complete validation report and easy modification and customization of the report document.

This section lists all checkpoints with their planning options and a short explanation of their meaning.

Precision

Precision describes the extent of conformity between results obtained during repeated use of a set analytical method under recurrent and comparable conditions. Monitoring the precision records random errors. Precision can be planned as precision in the true sense, or as repeatability from linearity. In both cases, the nominal (expected) values of the variation coefficient can be entered. Further precision can be used to determine the stability according to ICH Q1A and Q2B. The purpose of stability testing is to provide evidence on how the quality of a substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the substance and recommended storage conditions. Stability according to Q1A is used for proving long-term stability, i.e. that an analytical substance is stable within a given range, normally for a period of 12-35 months. To do so, a linear regression is calculated and the extrapolated regression values as well as the extrapolated values of the confidence interval are compared against the acceptance period. Stability according to Q2B is used for proving short-term stability, i.e. stability of the analytical substance (typically 24-48 hours). In both cases the study duration, the initial value (initial amount or response of a freshly prepared standard) and the specification limit in percent (acceptance interval) are entered. For long-term stability a minimum storage duration as acceptance period is additionally specified. Precision can be performed with multiple injections as well as multiple determinations. Figure 38 shows the planning dialog for checkpoint "precision".

Planning data

- Determination method:
  - Precision
  - System precision from linearity
  - Stability test
- Other data
  - Number of values (change default)
  - Y-units
  - Multiple injection possible

Output settings

- Repeatability limit
- T-value
- Confidence interval
- Error of result
- Trend test according to Neumann
- Outlier test according to Dixon/Grubbs
- Normality check (Sharpiro-Wilk-Test)
- Method standard deviation
- Mean value
- Correlation coefficient

Robustness/Ruggedness

Robustness is defined as the independence of an analytical result from changes in other parameters, which could influence the result. Ruggedness of an analytical method is given if the deviation of laboratory mean values is not significantly different from the deviation of all measured values. Ruggedness should show the reliability of an analysis with respect to the influence of transferring a method to another

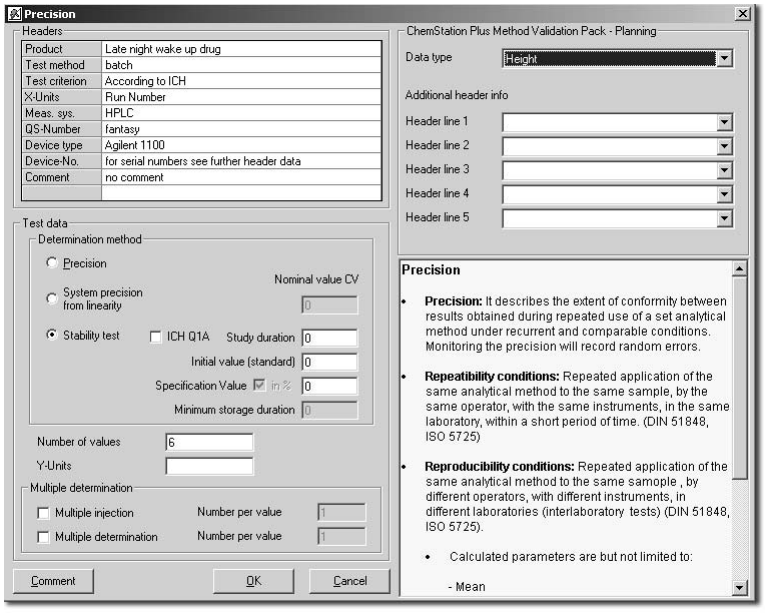


Figure 38
Planning dialog for checkpoint "Precision"

instrument. Sometimes both terms, robustness and ruggedness, are used interchangeable. Whether or not a method is considered as robust/rugged is distinguished by the fact that a change of parameters (method setpoints, environmental conditions, instrument etc.) within a reasonable range has no significant influence on the result. The F-test and the t-test can be applied as statistical criteria for the evaluation. As a measure for ruggedness, the comparative standard deviation is calculated and listed. Figure 39 shows the planning dialog of the checkpoint "ruggedness/robustness".

Planning data

- Determination method:
  - Comparison of results
  - Comparison with reference
- Other data:
  - Number of series (from 2-50)
  - Y-units
  - Multiple injections possible
  - Nominal value for the standard deviation

Output settings for calculations

- Comparison of results
- Neumann trend test
- Dixon or Grubbs test for outliers
- Variance homogeneity
- Repeatability limit
- Reproducibility limit
- Error of result
- Range of confidence (repeatability conditions)
- Range of confidence (reproducibility conditions)
- Test for robustness
- Comparison with reference
  - Apply t-test
  - Apply F-test

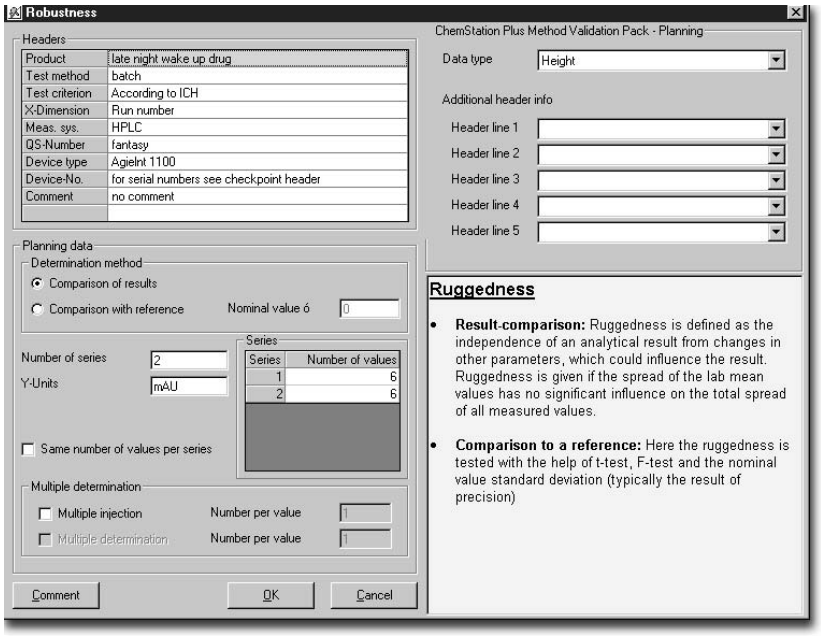


Figure 39
Planning dialog of checkpoint "Robustness/Ruggedness"

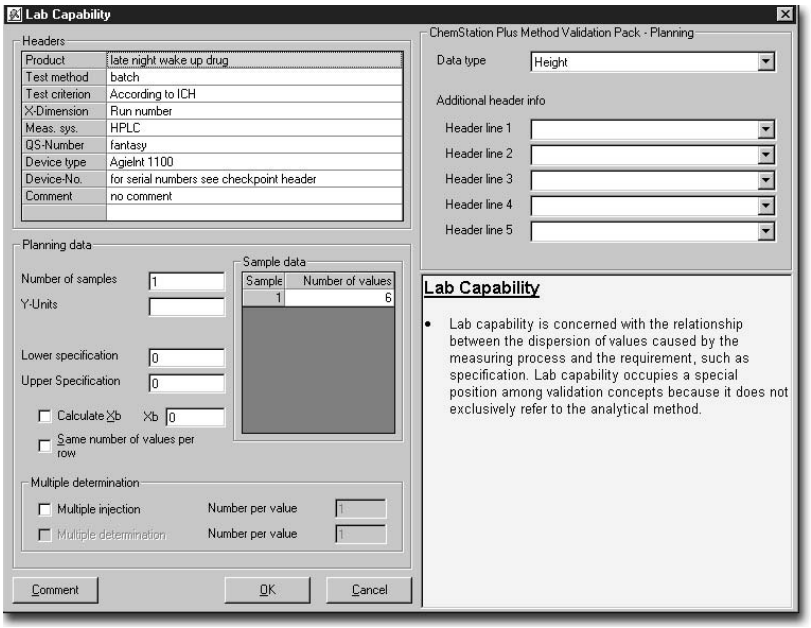


Figure 40
Planning dialog of checkpoint "Lab Capability"

The following results are always calculated for robustness/ ruggedness testing:

- standard statistics such as mean value, RSD, repeatbility and reproducibility along with confidence intervals for repeatability and reproducibility, and
- variance homogenity according to Bartlett.

Lab capability

Knowledge of lab capability is necessary for accurate estimates of process capability (see DIN 55350 parts 33 and 11). Lab capability is not required by the FDA nor ICH. It checks for the ratio of result dispersion versus specifications. Lab capability occupies a special position among Validation concepts because it does not exclusively refer to the analytical method. Figure 40 shows the planning dialog of checkpoint "linearity"

Planning data

- Number of samples
- Y-units
- Lower specification
- Upper specification
- Calculation of Xb, where Xb is the reference value (expected analytical result value)
- Multiple injections possible

Output settings for calculations
No output settings can be configured by the user. For lab capability, the lab capability index Cm and lab performance index Pm are determined, as well as the corrected values Cmk and Pmk. The result includes all indices along with the specification limits and a judgement if lab capability is low, medium or high.

Linearity

Linearity calculates a linear regression using the least square error for the model y = a + bx. Linearity calculations can be carried out for multiple injections and multiple determinations. Figure 41 shows the planning dialog of the checkpoint "linearity".

Planning data

- Determination method:
  - Regression weighting: unweighted, weighted 1/x, weighted $1/x^2$ or
  - Proportionality (test for validity of one point calibrations)
- Other data:
  - Number of levels
  - Y-units
  - Multiple injections possible
  - Multiple determinations possible

Output settings for calculations

- Residual standard deviation
- Method standard deviation

For proportionality the following entries need to be specified: the nominal value d, which describes the maximum deviation of the one-point calibration from the linear regression, the niveau specification limit g, which is the minimum concentration where the one-point calibration has to be valid, and the number of measurements to be executed at the limit g. Calculated parameters are:

- Sum of the x- and y values
- Slope
- y-intercept
- Linear equation
- Residual standard deviation
- Absolute method standard deviation
- Relative method standard deviation
- Confidence interval of the slope and y-intercept
- Coefficient of correlation (r)
- Coefficient of determination (r^2)

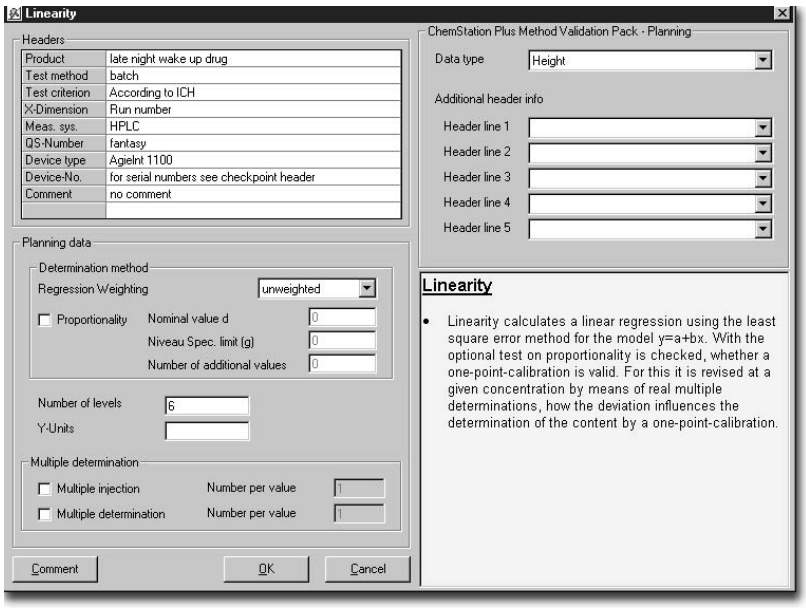


Figure 41
Planning dialog of checkpoint "Linearity"

Calibration function

The calibration function is the correlation between the expected value of the test characteristic, e.g. the UV absorbance (see DIN 55350 part 13), and the content, e.g. a concentration. The user can specify the maximum degree of curve fit for the calibration curve. 1st order is standard and 3rd order is the maximum (cubic curve). Figure 42 shows the planning dialog of the checkpoint "calibration function"

Planning data

- Number of levels
- Unit of values
- Curve fit display 1-3
- Multiple injections possible
- Multiple determinations possible

Output settings for calculations

- Vector y=ax+b - curve equation in the case of linearity
- Square sum of the residuals (only calibration function)
- Residual standard deviation
- Mean value and standard deviation of y
- Multiple correlation coefficient
- Results of F- and t-tests
- Method standard deviation

Limit of detection and limit of quantitation

The detection limit (LOD) is the smallest amount of substance that can be detected qualitatively during one analysis with a defined statistical certainty. The quantitation limit (LOQ) is the smallest amount of a substance that can be detected quantitatively during one analysis with a statistical certainty to be determined. The quantitation limit is higher than the detection limit. The relative error of results is requied to calculate the quantitation limit. Both the d etection limit and the quantitation limit can be calculated by the standard deviation of blank values (blank value method) or the residual standard deviation of regression data (calibration curve method). Only one of the two methods may be suitable for practical purposes. Both methods, however, are almost equal with respect to the detection limit. The calibration curve method is suited to determine the quantitation limit. For this method the concentration and the slope values need to be entered during data entry. If the blank value method is chosen, the user must enter or import the measured values and the value of the slope of the calibration function. Further the ICH-guideline describes a calculation of LOD and LOQ based on the standard deviation of the signal and the calibration curve (slope). This is referred to as "according to ICH" in the planning dialog. Finally LOD and LOQ can be determined by "visual inspection" based on the signal-to-noise-ratio. In this case no calculations are performed and the chromatogram is attached to the validation as a bitmap (BMP format) or windows meta file (WMF format) and included in the overall report. Figure 43 shows the planning dialog of the checkpoint "limit of detection/quantification"

Planning data

- Determination method:
  - Blank value method according ICH
  - Calibration line method according to ICH
  - ICH method

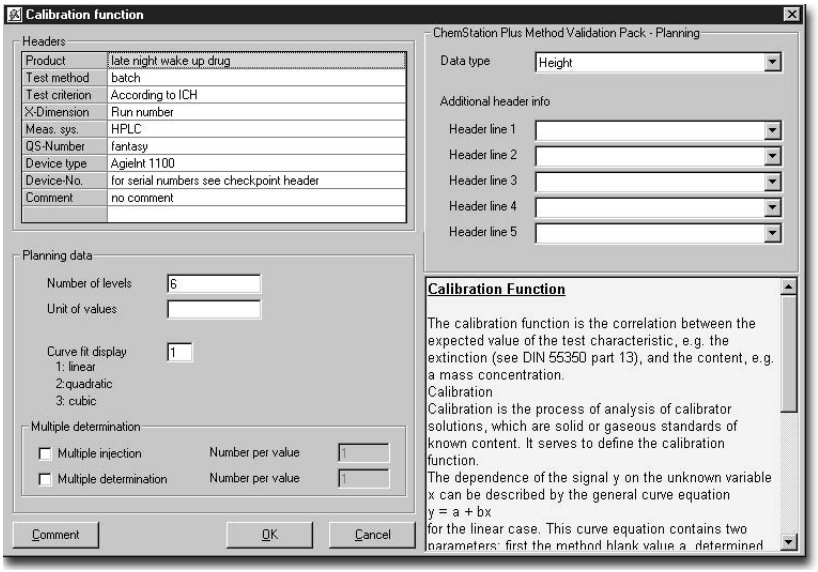


Figure 42
Planning dialog of checkpoint "Calibration Function"

- Signal/noise ratio according to ICH
- Other data
  - Nominal values for the detection limit d and quantitation limit q
  - Number of samples
  - Y-units
  - Multiple injections possible

Output settings for calculations
- Standard deviation
- Procedure standard deviation
- Critical value yk
- Residual standard deviation (additional for calibration curve method)

Accuracy

Accuracy is a qualitative measure describing the extent of correspondence between the expected value and the conventional value. Accuracy is influenced by systematic errors. The systematic error is divided into a constant systematic error and a proportional systematic error. A constant systematic error is not influenced by the concentration of the substance to be determined. If the error is influenced by the concentration, it is a proportional systematic error. A qualitative measure for accuracy of a result is its systematic deviation. Figure 44 shows the planning dialog of the checkpoint “accuracy”. Method Validation Pack provides a set of different determination methods, some involving a comparison with a second method. The standard addition method is used in trace analysis and determines the matrix influence. The extended spiking method allows constant and proportional systematic errors to be determined, even when there are no samples with known

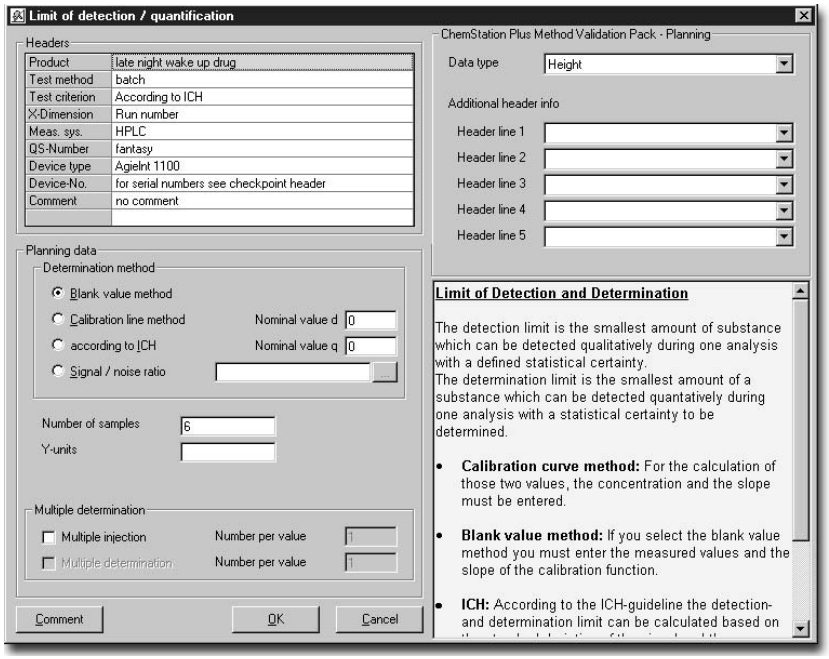


Figure 43
Planning dialog of checkpoint “Limit of Detection/Quantification”

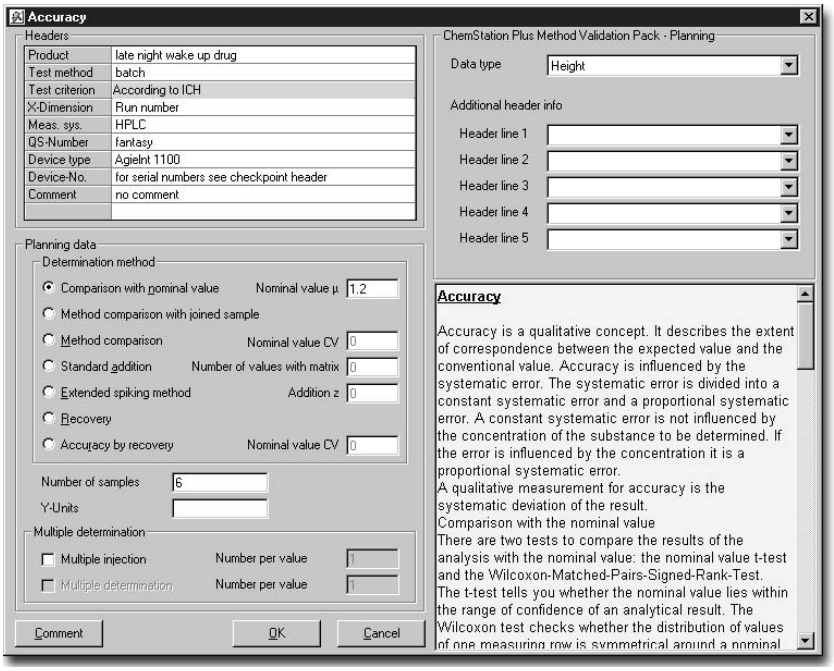


Figure 44
Planning dialog for checkpoint “Accuracy”

content. It is suitable for analytical methods which consist of weighing, diluting and measuring steps. For the recovery method linearity must be given for a number of samples with different content. A nominal value for the variation coefficient VC can be entered for method comparison and for accuracy by recovery.

Planning data
- Determination method:
  - Comparison with nominal value µ for the t-test
  - Method comparison with joined samples (two sample sets determined with two different methods)
  - Method comparison with a validated method (according to ICH)
  - Standard addition
  - Extended spiking method
  - Recovery
  - Accuracy by recovery (according to ICH)
- Other data:
  - Number of samples
  - Y-units
  - Multiple injections possible

Output settings for calculations
- General:
  Result t-Test
- Joined samples:
  - Difference of value pairs
  - Mean value and standard deviation of differences
- Nominal value comparison:
  - Result of Wilcoxon test (additional for nominal value comparison)
- Extended spiking method:
  - Test quantity for a and b
  - Threshold quantity t division
- Standard additional method:
  - Result F-test
  - Result t-test
- Recovery
  - Standard deviation for a, b
  - Residual standard deviation
  - Method standard deviation
  - Test quantities ta and tb
  - t-distribution
- Method comparison
  - comparison of mean values

Selectivity/Specificity

Selectivity means that an analytical method can distinguish the substance to be determined from other substances in the sample. Specificity is a synonym for selectivity, selectivity in chromatography describes the separation capability of the chromatographic system for two components. Figure 45 shows the planning dialog of the checkpoint "selectivity". The selectivity is determined from the resolution values calculated by the ChemStation. Available calculation methods are tangent (according to USP, EP and ASTM), sigma, halfwidth and statistical.

Planning data
- Number of values
- Y-units
- Nominal value for the resolution R
- Add chromatogram bitmap
- Multiple injections possible

Output settings
All available data including the obtained resolution values are shown.

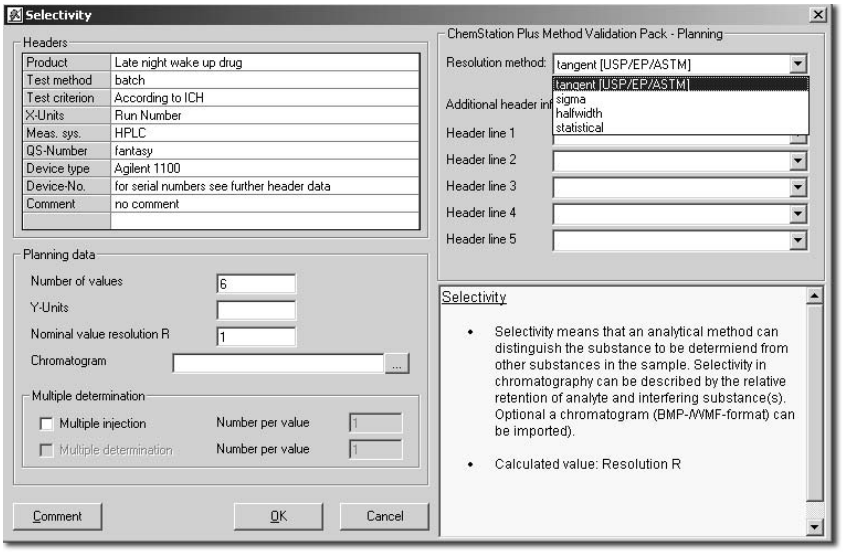


Figure 45
Planning dialog of checkpoint "Selectivity"

Ring experiment

Ring experiments are used to prove that a method can be successfully transferred to an entirely different location (other site, company etc.) and that it delivers appropriate results. A ring experiment can be seen as a more general ruggedness test. Figure 46 shows the planning dialog of the checkpoint “Ring experiment”.

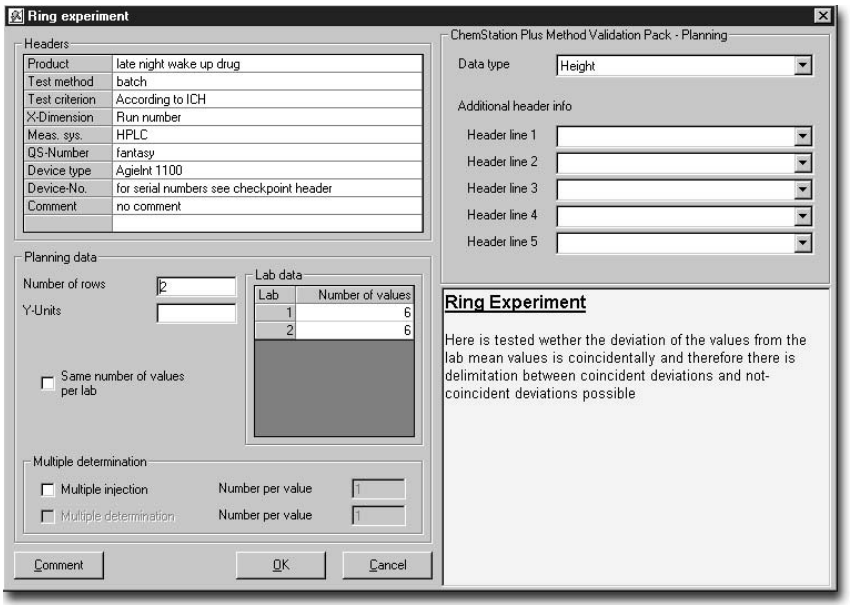


Figure 46
Planning dialog of checkpoint “Ring Experiment”.

Planning data

- Number of rows (one row for one lab)
- Y-units
- Checkmark for same number of values per lab
- Multiple injections possible

Output settings

- Neumann trend test
- Dixon or Grubbs test for outliers
- Variance homogeneity
- Repeatability limit
- Reproducibility limit
- Error of result
- Range of confidence (repeatability conditions)
- Range of confidence (reproducibility conditions)

All output settings are preconfigured during installation to useful defaults. As long as you do not have the need to enable special settings, there is no need to change anything.

ChemStation Plus Method Validation Pack — Interaction with other ChemStation Plus modules

As described in previous sections Method Validation Pack interacts with ChemStation for data acquisition and ChemStore for result and data management.

Interaction with ChemStation for data acquisition

If Method Validation Pack is installed in a ChemStation Plus data system ChemStation will offer additional functionality to run and execute method validation sequences. It includes two additional Method Validation menu items in the ChemStore menu (figure 47), as well as new buttons in the graphical user interface. The first button switches ChemStation into method validation mode and back to the standard mode. The second button opens the sequence import dialog.

If method validation mode is enabled, the user has access to the method validation sequence import menu. The import window displays a list of all pending method validation sequences (MVS files) the user should have access to. The list includes status information and user assignment of the MVS files. In a client-server installation the list of method validation sequences is accessible from any ChemStation in the cluster that has Method Validation Pack installed. This means that validation planning

and data acquistion do not need to be done on the same system. Users can now select the MVS files they want to download from the list of pending files. An MVS file has an assignment to one specific user or it has no user assignment and is thereby an all-user job for all users with a valid logon an the appropriate access privileges to Method Validation Pack. As soon as a user has loaded a pending validation sequence for execution in the ChemStation, it is blocked for other users. Before running the sequence the user can add additional sequences lines, for example calibration runs, blank runs or system suitability checks. Partially completed MVS sequences can be set to *Finalize* which skips the remaining acquisition runs and deletes the file from the list of pending MVS files. The missing runs can be executed at a later point in time by submitted them again in a custom sequence. Alternatively partially executed and not finalized MVS sequences can be reloaded and re-run after the already executed sequence lines have been manually deleted. Finalizing a MVS sequence will also lock the validation and prevent it from further modification.
A validation can only be unlocked by an authorized user and requires an electronic signature.

MVS sequences are created with a specific command (*Create Study and MVS for ChemStation Plus*) in the Method Validation Pack software. They are automatically built according to the validation configuration in the Method Validation Pack software - no user interaction is required. The MVS sequence template is stored as a text document with the validation in the Document Management System (DMS) of the Method Validation Pack software. Each injection translates into one line in the sequence table; repetitive injections of the same sample receive only one sequence line but write the number of injections in the related sequence column. The MVS files automatically include information on the sample type, number of injections and sample name. The sample name references the related checkpoint, the sample comment contains more detailed information. By default the method name in the method column of the sequence table is populated with the validation name. It will have to be replaced with the real name - especially when several methods are required, for example during robustness testing. A convenient way to quickly fill in the method name is the sequence filldown wizard of the ChemStation. Additional information is stored in protected custom fields. This information displays the checkpoint name, the component name and a unique run-ID for easy identification in the sample information text dialog. These fields can only be configured and edited by the Method Validation Pack software.

To run MVS sequences the operator only fills in the vial position for the samples and starts the sequence. For further details on ChemStation functionality, please refer to ChemStation specifications, Agilent Technologies publication number 5988-5314EN.

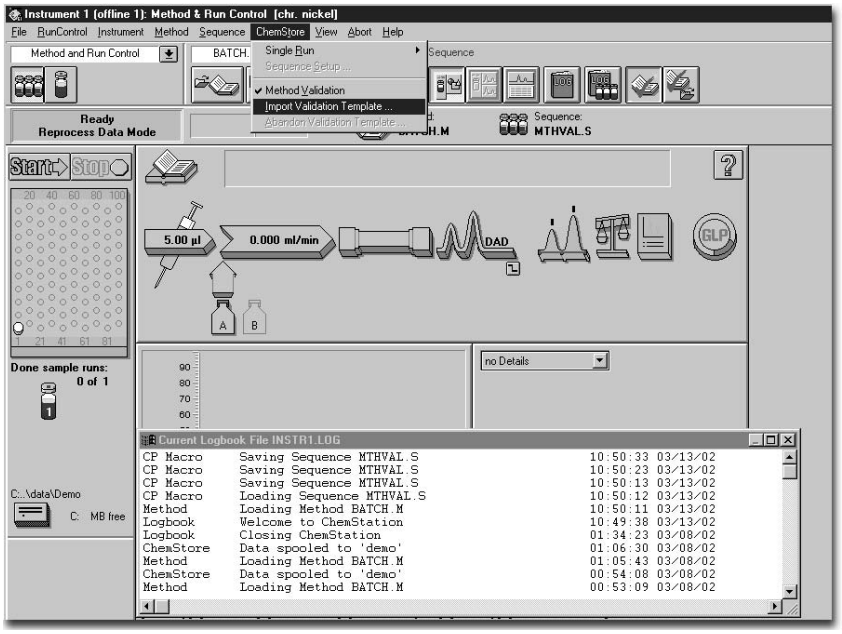


Figure 47
Additional Method Validation menu item in the Data Acquisition ChemStation software module

Agilent ChemStation Plus Method Validation Pack — Interaction with other ChemStation Plus modules

Data management

ChemStore manages the analytical results along with the raw and meta data of the samples in a relational database. This also includes all analytical data of the method validation sequences that have been acquired in the ChemStation. The method validation data are stored in method validation-specific studies. Method validation studies are similar to standard ChemStore studies except that they can only be created and modified through the Method Validation Pack software. All method validation study data are visible in ChemStore, but they can not be changed or modified except for reanalysis. As part of the data transfer from Method Validation Pack to ChemStation the Method Validation Pack software creates and, when revising data, updates a method validation study in ChemStore. The study name corresponds to the validation name. It is recommended to use short validation names as a study name is limited to 12 characters. Method Validation studies have three custom fields automatically configured with the studies. These fields are

- MV_checkpoint - storing the Method Validation Pack check point information (which test was used with this run)
- MV_component - the name of the Method Validation Pack component in the validation - comparable to the ChemStation Plus compound.
- MV_runID - storing a unique run identifier that allows full traceability from method validation pack results to ChemStation Plus result management. This is particularly useful for example, if you notice outliers in your method validation. In order to check the integration and decide whether to reanalyze this run, you only have to query for the run-ID to immediately obtain the run that is under investigation with its result.

Data review

A first pass review of the data is done in the ChemStore review client. Here the user can inspect the results and the quality of the integration. The graphical result review such as inspecting the baseline of the chromatogram or zooming in to check the integration is done in the chromatogram view of the review client. If any rework is required the data can be submitted to the ChemStation batch review user interface for graphical rework and data reanalysis as described in the section *Agilent ChemStation Plus Security Pack - Graphical Result Review and Calculation.* These steps generate a new result version that is then used for the validation instead of the initial version. If a result was obtained by applying manual integration events it will be marked as such in the validation report. The result is transferred to the database and the change is documented in the run-related audit trail.

The user decides if the validation is a development validation or a final validation that must run under full 21 CFR Part 11 conditions. In the former case, users with administrative rights can configure the level of audit trail for the validation and the study settings of the ChemStore study. This is done within the Method Validation Pack and is similar to the study configuration in ChemStore. They can select to

- Save raw data with results
- Delete raw data on the local hard disk after transfer to the database
- Save method and sequence along with results
- Save chromatogram and spectra pictures with the result

In a 21 CFR Part 11 validation, all these functions are enabled for the data management options and cannot be disabled. The validation report includes a marker which clearly indicates whether the validation was a carried out unter 21 CFR Part 11 conditions or, under less stringent conditions, as a development validation. If the decision was made to run a validation in development status in order to reduce the amount of information stored in the database and logged in audit trails, this decision cannot be revised at a later stage. A development validation cannot be promoted to a 21 CFR Part 11 validation.

Based on the hierarchical structure of the Method Validation Pack software, the system has five user levels. They are:

1) *Reporting:* Logging into the system with a name and a password of level 1 (reporting) gives the user access to report output only. At this level, data changes are impossible.
2) *Data input:* Logging into the system with a name and a password of level 2 (data input) gives the user access to all level 1 tasks and validation data input (loading study data, manual input, import) and the configuration of the graphics/report output.
3) *Planning:* Logging into the system with a name and a password of level 3 (planning) gives the user access to all level 1 and level 2 tasks plus checkpoint planning.
4) *Configuration:* level 4 (configuration) gives the user access to configuration rights and all level 1-3 tasks. The user may change the configuration on a validation level only.
5) *Administration:* Logging into the system with a name and a password of administrator level 5 gives the user access to all functions of Method Validation Pack including the program configuration (global settings such as the default validation settings for new validations).

The user levels are part of the ChemStation Plus user administration as shown in figure 48. They are centrally configured and administered in the ChemStore database. All users have two identification components, user ID and password. One user ID is valid for all ChemStation Plus modules, so a user only has to remember one password for all tasks he is assigned to in ChemStation Plus.

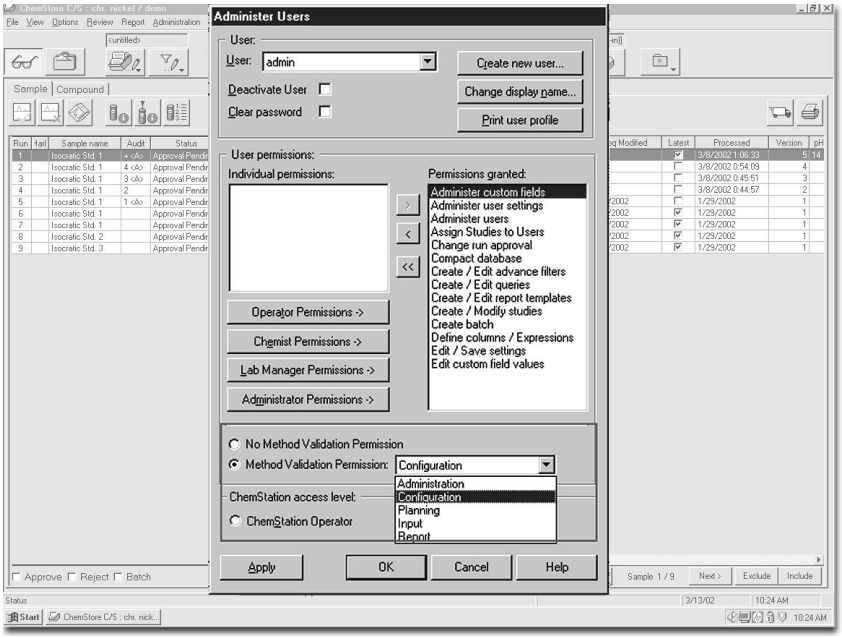


Figure 48
Central user administration for ChemStation Plus including Method Validation Pack user administration and user levels

User authorization

As mentioned under “User management”, only users with a valid ChemStation Plus user ID and password can log on to the Method Validation Pack software. The user management includes a password policy for regular password renewal and user account lockout after a specified number of unsuccessful password entries. For details, please refer to ChemStation Plus Security Pack specifications.

Document management system

Method Validation Pack comes with a fully featured document management system (DMS) storing all data in a relational Oracle database. For standalone systems, all data are stored in a VDB file, a database file that adheres to a common file format as used by MS Access. The DMS is automatically started with Method Validation Pack and runs in the background. It is used to store and maintain validation data by providing full versioning of validations and storage of all important related data such as configuration and planning information, document attachments, copies of reports and validation sequences that were generated for full traceability. It stores all data under the validation name as the highest hierarchical element called “document”. It is subdivided into four subsections as shown in figure 49:

- VDB section for *validation data base*—all data from planning, configuration, setup and analytical results.
- MVS section for *method validation sequences*—all ChemStation method validation sequences that have been created from the validation database.
- DOC section for *reports*—all reports are stored as doc files that have been printed for the validation database.
- PDF section for *reports in pdf-format*—all reports exported in pdf-format for this validation are stored in this section.

Each section offers a full revisioning of the data. Whenever a new entry in the DMS is made, a new revision is created. The revision is uniquely identified through continuous version numbers, the timestamp of creation along with the user name, the database name and the PC host name. Each revision of each file can be recreated and reopened for review. All DMS entries are displayed in a hierarchical list. Entries can be selected to view all properties which are displayed on the right window pane of the DMS. Additional information that is stored with each revision includes:

- name of entry,
- original path,
- label,
- purpose of entry (manual revision, automatic revision),
- version,
- document type,
- size,
- checksum,
- status (normal, checked-out and finalized),
- login of user, user domain and user computer,
- real name of user (display name),
- reason for check-in,
- check-in date, and
- date of parent entry (i.e. base node entry).

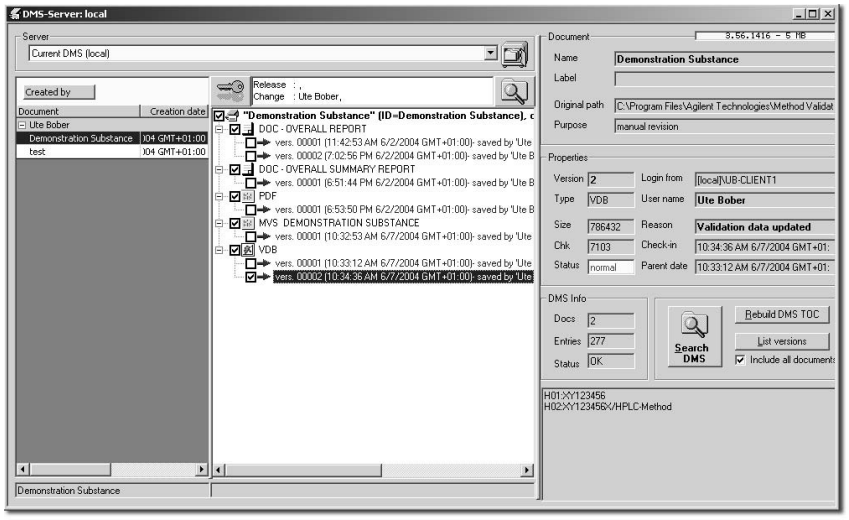


Figure 49
Method Validation Pack document management system DMS

A click in the checkbox of a section offers review of any document revision. Clicking a version child node once displays its properties. Double-clicking a validation (VDB-file), or clicking on its selection field, will restore the selected version. Documents and MVS files can be displayed in a review window, allowing to zoom, print, export or copy the selected document. The actions depend on the type of entry: documents are displayed in a review window, validations are stored in the file system.

DMS with standalone systems
Standalone systems will typically require managing multiple databases. The system will prompt the user to create a new DMS database file after the size limit of 800 MB is exceeded. A DMS or validation that has passed its size limit can still be selected for review. If the system has more than one DMS database, the user is automatically connected to the current DMS as shown in figure 50. If there is a need to review old data the user has to select the DMS database from the dropdown list of available database to connect to it. The DMS databases are sorted and named by date.

DMS for client/server systems
Client/Server system using an Oracle relational database will store all validations in the same database. A list of all available validations displays when selecting to open an existing validation. The user selects the validation from the list with a simple click on the actual validation. If users open older revisions of a validation the validation is opened in a locked status as read-only. Only saving it as the latest revision removes the read-only lock.

Figure 50
Selection dropdown window for database connection

File security for the standalone database

The local validation database must be protected from unauthorized access for example through Explorer or MS-DOS. Method Validation Pack software uses file security settings to protect the database file. All Method Validation Pack data is stored under the Method Validation Pack root directory on the PC hard drive. The Document Management System is located in a separate subfolder of the Method Validation Pack program directory. The folder name is DMS. This folder is protected with Windows file and folder permissions. It offers write-only access to all authenticated users and only an administrative user has full access to the DMS directory. Understanding and using file security is particularly important in standalone installations where all data is stored in the local database. In a client-server installation, the default storage location should be the Oracle database that is stored on a separate server and that is not accessible to any software operator.

Permanent display of current user

Method Validation Pack always displays the current user in the title bar. The system displays the current user name and the database information. The database is either displayed as local login for a standalone database connection or as the Oracle database alias if the system is connected to an Oracle database, as shown in figure 51.

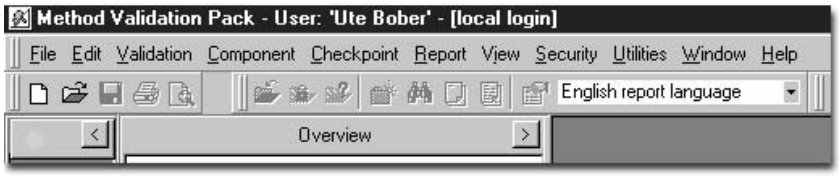


Figure 51
Permanent display of current user name, and database connection with Method Validation Pack software

Audit-trails

The Method Validation Pack audit-trail tracks all actions that users execute during program operation. The audit-trail is user-independent, can not be modified nor deleted and it is completely system-generated. Method Validation Pack has three different audit-trail levels, as shown in figure 52:

- program audit-trail,
- default validation audit-trail, and
- validation audit-trail.

The default display size of the audit-trail can be configured in the audit-trail window. The number of entries for display must be between 25 and 30000. All audit trails can be printed to a printer. The validation audit trail can also be included in the overall validation report. This is a global setting and has to be enabled for generating the report.

For easier searching through the audit trail, users can group the audit-trail entries. All audit-trail column headers are available as grouping criteria. The grouping functionality uses a simple drag-and-drop functionality to enable or disable grouping. The user only drags the column header into the grouping section and receives a sorting of the complete audit-trail according to the column entries. As an example, the audit-trail should be arranged by user name. The system displays all user name entries as parent nodes. A simple click on the node expands the audit trail to now display all audit-trail entries for the selected user as shown in figure 53.

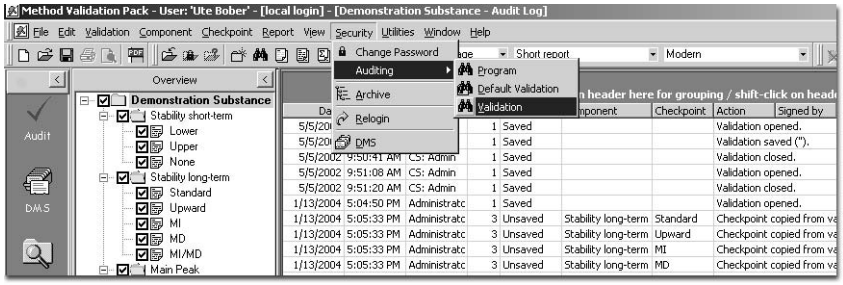


Figure 52
Three levels of audit-trail with Method Validation Pack software

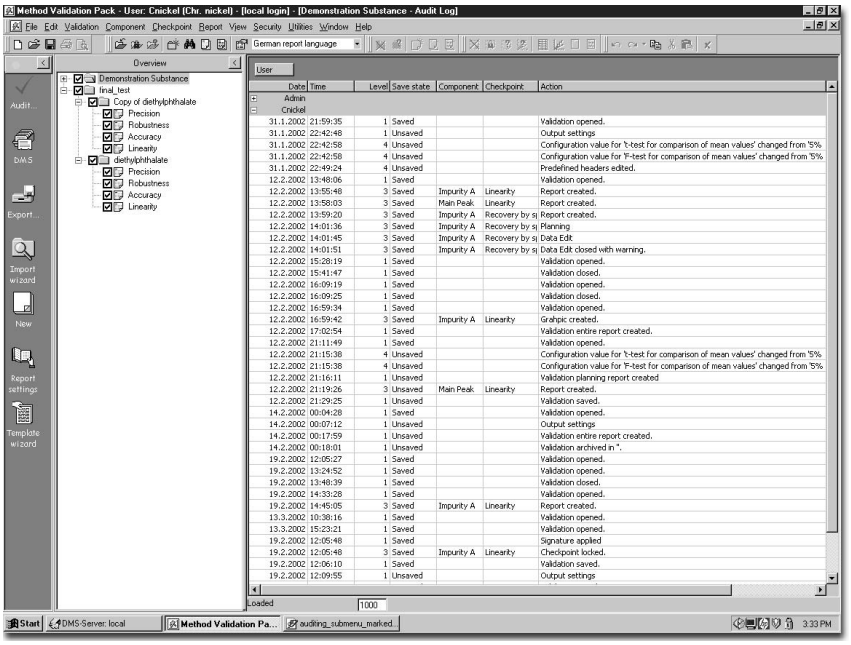


Figure 53
Grouping of audit-trails, in this example grouped by user

Audit-trail details

The validation and default validation audit-trails display all actions that are related to a validation or the default validation template which is applied when creating new validations.

Both audit-trails offer the following information where each item displays its data in a separate column:

- Date and time of action
- Printed user name
- Level of action (e.g. level 4 for configuration changes)
- Status of the change (saved or unsaved
- Affected component
- Modified checkpoint
- Action (the audit-trail lists the menu if the user did only open the menu without changes and it lists any parameter change with the old and the new value)
- Display name of the signer and signature comment

The program audit trail will be described in more detail in the following section.

Default validation audit-trail

The default validation audit-trail refers to the general configuration of validations. It covers all changes that are not related to a specific validation database but apply to the validation template that all new validations are based on upon creation. These settings are new validation properties and new validation output settings. Changes to these settings are displayed in the default validation audit-trail.

Validation audit-trail

The Validation audit-trail tracks all actions on the actual validation.

Program audit-trail

The program audit-trail is designed to track all actions that relate to the general program operation such as save and logon actions. The program audit-trail table items are:

- Date and time
- User ID
- Validation name
- Storage location of the actual validation snapshot copy
- Action (Program start and stop, user logon and logoff, IQ execution, validation opening, use of import mask for data entry, and program options)

Validation locking and electronic signatures

After completion of a single checkpoint, an entire component or a complete validation, a validation can be locked to the same extent to prevent further modification. To avoid locking of incomplete items, the application software will display a warning message and close the lock dialog without changes if the locking procedure was not completed by giving an electronic signature.
Partial validation locking allows locking a single checkpoint or a complete component. After locking the item, no changes are possible to this particular item anymore, unless it is explicitely unlocked. It is in a review-only mode allowing only printing reports and reviewing the graphics. Every locking action automatically creates a new revision of the validation in the DMS system. Only users with an access level 3 (planning) or higher have access to the locking functionality. Each locking action requires an electronic signature. The electronic signature uses the password/ user ID combination as defined by the FDA (figure 54). The sign-off dialog comes with a time limit of 45 seconds. If the signature was not executed during this period, the dialog will close and the validation status remains unchanged.
If an item was locked by mistake or has to be modified due to late changes in the test specifications the lock status can be removed by a user with sufficient privileges (level 3 or higher). For unlocking a validation, component or checkpoint the same procedure is followed as for locking. The user has to give an electronic signature to initiate unlocking.

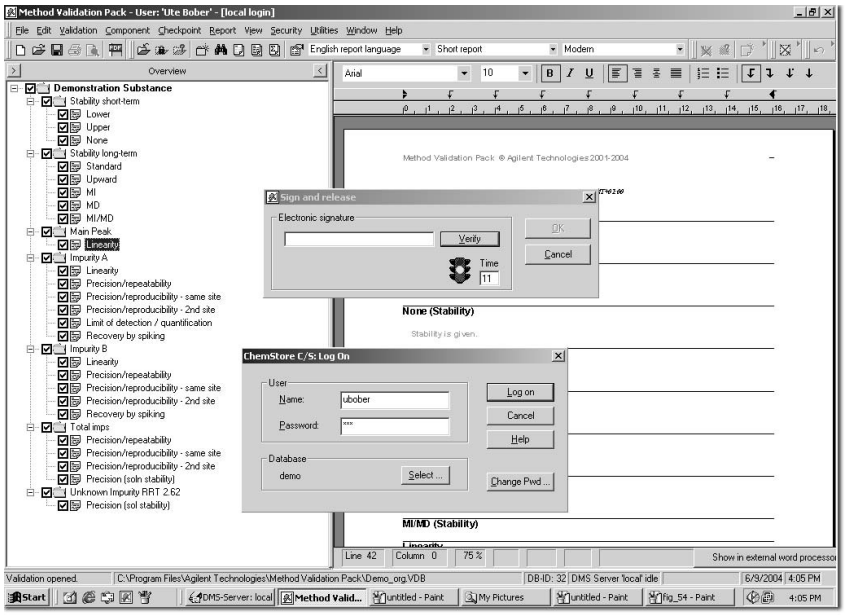


Figure 54
Executing electronic signatures with Method Validation Pack

Prerequisites

Method Validation Pack can operate both PC-based in a standalone installation or in a networked system installation with full client-server functionality. In both scenarios, some prerequisites must be met:

Software

ChemStation Plus standalone – For a fully integrated installation of Method Validation Pack it is required to have the following software installed:

- ChemStore standalone rev. B.03.01 or higher or Security Pack rev. B.03.01 or higher and
- Agilent ChemStation for GC, LC, A/D, CE, CE-MS and LC-MS rev. A.10.01 or higher for data acquisition

ChemStation Plus

If the system should operate in client-server mode, ChemStore with Oracle 9i (version 9.2.0.3.0) must be installed on the system. In the client-server installation, all ChemStation Plus modules can operate from different PCs. Their installation is completely independent and the system is fully functional as long as all required modules (see above) are installed within this cluster and they can connect with each other.

Non-Agilent software

- MDAC 2.8 (Microsoft Data Access Components 2.8) (installed by ChemStore)
- Adobe Acrobat Reader 5.0 (part of standard bundle)
- Microsoft Internet Explorer 6.0

The Microsoft Data Access Components install a layer to access local databases or central database servers. Method Validation Pack uses Microsoft JET database to save local data (i.e. Microsoft Access format). Adobe Acrobat Reader 5.0 is required to display the online manual.

Standalone installation

The standalone installation is user installable from the Method Validation Pack (rev. A02.01 or higher) software CD-ROM. All other ChemStation Plus modules as outlined above are also user installable for advanced users. However, Agilent recommends the installation of the ChemStation Plus modules through an Agilent-certified service engineer to prevent from any potential installation problems and for inclusion of software familiarization upon installation.

Client-server installation

The client-server installation must include for the server

- installation of Oracle 9i server software (version 9.2.0.3.0) ,
- installation of ChemStore server software,
- creation of the Oracle database
- installation of Method Validation Pack software, and
- creation of Method Validation Pack tablespaces in ChemStore Oracle instance (alias “HPCS”)

On every client the procedure includes the installation of

- Oracle 9i client software version 9.2.0.3.0
- ChemStation software for data acquisition
- ChemStore or Security Pack software for data management
- Method Validation Pack software

Please note that Method Validation Pack software does not necessarily need to be installed on every client in a client-server system. If method validation is carried out on a subset of all networked ChemStation Plus clients, only those clients participating in the process of validating analytical methods must have the software installed.

Agilent offers the complete portfolio of installation, validation and training through its project services organization. This will be handled as one project where the complete service delivery is managed centrally based on the individual customer requirements.

ChemStation Plus Method Validation Pack — Product Options and Configurations

Standalone version

The standalone version of Method Validation Pack requires the additional installation of the ChemStation for data acquisition and the ChemStation Plus database module for data management of analytical data. The database can be ordered as G2181BA ChemStore database or as G2183AA Security Pack for full support of 21 CFR Part 11. The installation only requires one of these products.

Description	Product No.
ChemStation Plus Method Validation Pack Requires but does not include ChemStore C/S or Security Pack. Allows for method validation according to DIN/ICH/USP and EP guidelines. Supports 21 CFR Part 11(only in conjunction with ChemStation Plus Security Pack).	**G2184AA**
Software module to add Agilent ChemStore C/S to an existing ChemStation for GC, LC, LC/MSD, CE or A/D.	**G2181BA**
ChemStation Plus Security Pack. Adds the secure ChemStore C/S relational database add-on software module to the ChemStation Plus SW for A/D, GC, CE, LC and CE/LC-MSD. Supports 21 CFR Part 11.	**G2183AA**

Client/server version

Method Validation Pack client/server installation runs on Oracle 9i Rev. 9.2.0.3.0. A complete system configuration requires ChemStore C/S server software (G1410A) for each server plus Agilent NDS Oracle user licenses (G1411A) for each named database user, one full use copy of the ChemStore client software (G2181BA) and a ChemStation Plus client license (G2186BA) for each connected client as well as copies of G2184AA for all Method Validation Pack clients. For full support of FDA's 21 CFR Part 11, replace G2181BA with G2183AA. Agilent provides all Agilent ChemStation Plus software and Oracle 9i software on Agilent CD-Rom media.

Description	Product No.
ChemStation Plus Method Validation Pack Requires but does not include ChemStore C/S or Security Pack. Allows for method validation according to DIN/ICH/USP and EP guidelines. Supports 21 CFR Part 11. Must have one copy of G2186BA or G2181BA per PC running Method Validation Pack software. For full support of 21 CFR part 11 replace G2181BA with G2183AA per server *NOTE: The number of Method Validation clients can be smaller than the number of ChemStation plus clients in case method validation will only execute on a subset of all networked ChemStation Plus clients*	**G2184AA** Qty: number of method validation systems in ChemStation Plus C/S networked data systems
ChemStore C/S server application software Includes ChemStore C/S server software, Oracle 8i standard edition software, 5 Oracle application-specific named user licenses	**G1410A** Qty: one per server
Oracle named user license for Agilent NDS Required for each named user of the ChemStore C/S server database	**G1411A** Qty: (Required for each named user in the ChemStation Plus networked data system) -5
ChemStore C/S client application software Software module to add Agilent ChemStore C/S to an existing ChemStation for GC, LC, LC/MSD, CE, CE/MSD or A/D.	**G2181BA** Qty: one per server
ChemStation Plus ChemStore client license Includes one online ChemStation Plus license for online data acquisition and one ChemStore C/S offline data review license. Includes license and user information only. Requires but does not include ChemStation Plus software client media.	**G2186BA** Qty: Number of clients -1
ChemStation Plus Security Pack. Adds the secure ChemStore C/S relational database add-on software module to the ChemStation Plus software for A/D, GC, CE, LC and CE/LC-MSD. Supports 21 CFR Part 11.	**G2183AA** Qty: one per server Replaces G2181BA

Installation, Qualification Services and Training

Installation and familiarization

Agilent Technologies' installation and familiarization service ensures that the Agilent ChemStation Plus is installed correctly and in the right environment.

In addition, Agilent offers a range of on-going support services to help:

- get your system up and running fast,
- resolve problems quickly,
- keep productivity high,
- extend instrument life, and
- comply with regulatory quality requirements.

Qualification services

- Agilent Technologies offers a full range of qualification services to provide the evidence you need to satisfy the requirements from agencies such as the U.S. Food and Drug Administration (FDA), the U.S Environmental Protection Agency (EPA), the International Standardization Organization (ISO), and the Organization for Economic Cooperation and Development (OECD).
- Installation qualification (IQ) service
- Operational qualification/ performance verification (OQ/PV) service

Training

Agilent's ISO-registered trainings can save you time, help keep your laboratory operating costs low, broaden your capabilities, and ensure that your laboratory complies fully with regulatory and quality requirements.
For your convenience, standardized courses are offered in selected locations worldwide. Onsite courses can be tailored to your specific needs.

www.agilent.com/chem/cds

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