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Specialized Considerations When Validating a CDS

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In this article I want to examine some of the specialized considerations for the validation of a chromatography data system (CDS). I'll start by looking at the key regulatory requirements, a life cycle approach to validation and finally outline approaches to defining and testing the adequate size and capacity of a client server CDS.

Req No.	Data System Feature Specification	Priority M/D
3.3.01	The CDS has the capacity to support 10 concurrent users from an expected user base of 40 users.	M
3.3.02	The CDS has the capacity to support concurrently 10 A/D acquisition channels from an expected 25 total number of channels	M
3.3.03	The CDS has the capacity to support concurrently 10 digital acquisition channels from an expected 25 total number of channels	M
3.3.04	The CDS has the capacity to control concurrently 10 instruments from an expected 20 total number of connected instruments	M
3.3.05	The CDS has the capacity to simultaneously support all concurrent users, acquisition and instrument connects while performing all normal operations such as reprocessing and reporting without significant loss of performance (maximum response time is <7 seconds from sending the request).	M
3.3.06	The CDS has the capacity to hold 20 GB of data live on the system.	M

Table 1: *Part of an Outline System Configuration for a CDS.*

Key Regulatory Requirements

I'll focus on the regulatory requirements of 21 CFR 211, the current Good Manufacturing Practice regulations and how these impact the design of the overall validation of any CDS. There are two specific regulations that I want to focus on.

The first is § 211.63 *"Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."* The key points to bring out here are the requirements for both appropriate design and adequate size, think how you have designed the CDS system operating in your laboratory environment and how you have shown that the size is adequate to support your laboratory.

The second regulation is §211.160 (b) *"Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures..."* Here you need to think of the tests that you have used in the performance qualification (PQ) testing to show that the CDS is fit for purpose and if they were scientifically sound.

However, we can't forget Electronic Records and Electronic Signatures final rule as this states in §11.10(a) *"validation of the system for accuracy, reliability, consistent intended performance and the ability to discern altered or invalid records"*. Consider a number of points:

• How your validation effort links with an on-going metrology programme for the calibration of the analogue to digital (A/D) converters used by the system

• Can the system distinguish altered records?

• Can the system detect invalid records?

• Is the performance defined and is it reliable?

We'll look at reliability and consistent intended performance in the context of this article.

Furthermore, the definition of Performance Qualification is *documented verification that the computer related system performs it functions in accordance with the computerised system specification while operating in its**normal operating environment.***[3]. The major point to make is that you have to test the CDS as YOU use it and not how the vendor has tested it (i.e. in your operating environment in the way that you work and to your

specification). Whilst, you can rely on vendor supplied material for the IQ and OQ phases of the validation, you'll need to demonstrate during the PQ that the CDS that you have installed and configured is of adequate size and has consistent intended performance. Moreover, the testing that you do must be scientifically sound.

Life Cycle Approach to Validation

A system development life cycle model is shown in Figure 1 and is in the shape of a V. The left hand side represents the design stages, the bottom is the programming and the right hand side is the testing stages of the life cycle. It is important to realize that there is a division between the user (above the line) and the vendor (below it). I'll focus on defining the requirements in the user requirements specification (URS) and testing them in the performance qualification (PQ), for more information on the system development life cycle and validation documentation, the article by McDowall [4]is recommended.

Specifying Your Requirements

You'll notice from Figure 1 that the user requirements are related to the tests carried out in the performance qualification. Therefore, it is important to define our requirements for adequate size and consistent intended performance in the URS.

Therefore, the first stage in our specialized considerations for validating a CDS is to define them in a URS. For our two main areas we need to consider some or all of the following requirements:

• Data capture rates across all chromatographic techniques connected to the CDS. For example conventional chromatography with a run time in the order of 20 minutes a data capture rate of 1Hz is usually adequate. However for capillary GC 10-20 Hz may be appropriate and for CE a higher rate may be required depending on the overall migration time and the analyte peak shape.

• Depending on your data system several chromatographs may be linked into a collection workstation or an A/D unit. Here you'll need to consider if crosstalk (the interference from one channel to another) could be an issue if the A/D chip is multiplexed across two or more channels and / or total sampling capacity of the data collection and buffering unit.

• Have you defined the maximum number of injections for an analytical run? This is a critical component, if you inject analytical batches with a 100 vials routinely, you can't validate the system with a run of only 10 samples as you have not demonstrated adequate size have you? The specification must match your use of the system, and don't forget any replicate injections.

• Some data systems will be configured to collect data from Diode Array Detectors (DAD). If this is required, especially to analyze product, then the data collection and analysis will need to be checked as part of the adequate size as some data files can be in the Mb range. By the way, do not enable the delete file option at the end of the run.

• Virtually all client server CDS systems will have a buffering capacity within their A/D or data collection units (if acquiring digital data from chromatographs by IEEE interfaces). Therefore, so part of the adequate size requirements must be the ability to capture and buffer data if the network is unavailable, followed by the successful transfer of data to the server when the network connection is re-established.

• How many users will you have on the system at the same time and will the system still perform its functions reliably? This number may be lower than the number of concurrent users that you have a license for but this is a major requirement to define in the URS and test during the PQ. If the system becomes unreliable or unstable as the number of users increase then you cannot state that the system has adequate size or can perform as intended.

These are some of the considerations for each installation of a CDS, once installed in your laboratory environment and on your organisation's network it becomes unique. The number of users, network components, server components, operating systems and patches and laboratory configuration make it so, therefore you need to demonstrate that it works under you operating environment.

Its all very well saying that a user has to define their requirements in a URS what does this mean? An example is shown in Table 1, this defines some of the possible system configuration items that can be specified but is not intended to be exhaustive. Note that each requirement is:

• Uniquely numbered

• Written to that it can be tested, if required, in the PQ

• Prioritized as either mandatory (essential for system performance) or desirable (nice to have and can be used without it). This prioritization can be used in risk analysis of the functions and also for tracing the requirements through the rest of the life cycle.

Remember as shown in Figure 1 that the URS functions are related to the tests carried out in the qualification phase of the life cycle. Therefore, if you have not specified the requirements how can you test it?

The question where in the qualification phase should you test a requirement depends on what is offered by the vendor in their IQ and OQ material. An objective way of deciding if the vendor material is worthwhile is to map it against your requirements, where there is a match use the vendor material where there is none you have to decide to take the regulatory risk and do nothing or formulate a PQ test.

Performance Qualification (PQ)

The PQ stages of the overall qualification of the system can be considered as the acceptance testing, undertaken by the users and based upon the way that the system is used in a particular laboratory. Therefore, your CDS cannot be considered validated simply because another laboratory has validated the same software: the operations of two laboratories may differ markedly even within the same organisation. The functions to be tested in the PQ must be based on the requirements defined in the URS and with the numbering of individual requirements can be traced back to this first document.

There are two approaches to testing: conventionally known as white box and black box testing.

• **White Box Testing:** This type of testing requires the full knowledge of what the program unit or module does including the complete specification of the inputs, and outputs and processing algorithms within each module of the CDS application. A user will not be able to undertake technical testing either because they do not have the full technical specification of the system or they do not possess the technical skills to undertake this type of testing or usually both.

• **Black Box Testing:** In contrast, in black box testing the tester only knows the overall function of the module with input limits. No programming knowledge is required but training in how to use the application is essential. Therefore, users will undertake black box testing, where known inputs will be entered and the outputs compared with that expected (anticipated results).

PQ Test Plan and Test Scripts

One way to document the is using an overall PQ test plan that outlines the features of the CDS to test and those that will not be tested and a discussion of the assumptions, exclusions and limitations of the testing undertaken. A documentation standard for the PQ test plan can be found in the IEEE standard 829-1983 [5].

In the same IEEE standard can be found the outline for the test scripts that are the heart of any PQ effort that I will focus my discussion on. The concept is that the test script will:

• Outline one or more test procedures that are required to test the CDS functions

• Each test procedure will consist of a number of test steps that define how the test will be carried out

• For each test step the results expected will be defined

• There will be space to write the observed results and note if it the test step passes or fails

• There will be a test log to highlight any deviations from the testing

• Sections will collate any documented evidence produced during the testing

• Definition of the acceptance criteria for each test procedure

• A test summary log collating the results of all testing

• A sign off of the test script stating if the script has passed or failed

Designing Capacity Tests for a CDS

Testing Overview

One key point is that to ensure that the PQ stage progresses quickly, a test script should test as many functions as possible as simply as possible (great coverage and simple design). Software testing has four main features, known as the 4Es [6]:

• Effective: demonstrating that the system meets requirements and finding errors

• Exemplary: test more than one function simultaneously

• Economical: quick to design and quick to perform

• Evolvable: able to change to cope with new versions of the software and changes in the user interface

So please bear in mind as we progress through this section, that you may be able to combine testing other functions into the capacity tests as well.

Manual or Automated Testing?

By the way, if you are tempted to use an automated test tool for your PQ execution consider Graham's words on the subject[6]:

• Automated testing tools take longer to use the first time compare to manual testing

• Expectation will exceed the delivery

• To be economical the test suite must be reused many times

• Best used for regression testing (to see if operation of the software remains the same after change)

• Automated testing is not a substitute for manual testing

My suggestion is don't use automated testing tools for the PQ as they will cause more problems than they solve. If a vendor offers an automated tool for the IQ and or OQ, then this will probably be useful, as it will establish if the system has been installed correctly and the software functions as the vendor intended it to. However, evaluate the

tool critically to see that it meets your needs and is compliant with GMP.

Outline Test Case Design

The considerations for designing stress and capacity tests for a CDS will be discussed here and will be based on the client-server architecture shown in Figure 2.

Analytical Run Capacity

First we'll look at an analytical run and the capacity test considerations we need to look at here. You'll know from the URS the maximum number of vials that you'll inject in a single run, this will include standards, samples, quality control and blank reagents that you may run as part of your normal procedures. A test should be designed to run the maximum samples including replicate injections.

Analogue to Digital Unit Capacity

Depending on the type of A/D unit this test can have one or more of the factors that we'll look at now:

• Crosstalk: if two or more channels are multiplexed through a single A/D chip, then a crosstalk test is recommended to see the impact of an overloaded signal on one channel impacts another.

• Data Acquisition Rate: compare the specified rata acquisition rate for a data server to the data rate of chromatographs attached to the unit including any diode array detectors.

In both or either of these instances you may decide that the total data rate is close to the specification of the unit and test this to ensure that the A/D unit is not compromised during normal operation. If the data rate is far below specification then an alternative path you may decide is not necessary to test and to document a rationale for this approach that is scientifically sound. Balancing the regulatory risks is one of the factors in computerised system validation, do you want to do this or test this function?.

Unavailability of the Network

There will be times when the network is unavailable and data will be buffered in the A/D unit or data server. You'll want to ensure that this function works during the PQ or you will have failed in your due diligence. The worst case example for the buffering will be defined in your URS and will be the number of injections with the longest run time. The run should be started, then the network is disconnected and the data accumulated in the A/D unit or acquisition unit until the end of the run when the network is reconnected and the buffered data are transferred to the server. There should be no loss of data integrity in any of the buffered and transferred files if this test is to pass.

System Capacity

The capacity of the system needs to be tested in a way that reflects on the way the system will be used and there are several approaches to take. If you have a 30 user license then one of the simplest ways of assessing the capacity is to run all systems simultaneously, however this will only test the data acquisition and transfer to the sever via the network. As the A/D units, buffer acquired data until transferred to the server this test will also implicitly evaluate the transfer with the network traffic at the time of the test. However, one of the main causes of performance degradation will be integration of data and this must also be included as part of any test of system capacity.

Reliability

Reliability over the number of users during the PQ, as described above, is one way of testing this parameter, but system reliability is really a long-term issue. The CDS needs to be monitored on an ongoing basis during its normal operation to ensure it performs adequately and any degradation is evaluated and assessed to see if any changes need to be made such as increase disc size or memory for instance.

Summary

Testing the adequate size of a client server chromatography data system requires a user to specify the required capacities in the user requirements specification to enable appropriate tests to be designed and executed in the performance qualification. These tests need to be scientifically sound and reflect the actual working practices of the laboratory qualifying the application.

References

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6. XX and D.Graham, Automated Software Testing, Addison Wesley, 1999

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